Kingdom Of Saudi Arabia
Ministry Of Health
General Deputyship for Laboratories and Blood Banks
General Directorate of Poison Control
and Forensic Chemistry Centers

Medical Toxicology Guide

Common Poisonings

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Preface 1

As a part of our commitment towards improving the quality of care and our mission to advance the practice of Medical Toxicology in the kingdom, we are proud to introduce this valuable document. In this practice guide, we hand-picked some of the most common poisonings encountered by health care providers in the kingdom.

We designed this document to be a quick and easy pocket tool that can guide physicians, pharmacists and nurses on how to effectively manage and stabilize acute poisoning cases along with the aid of a medical toxicologist. This guide incorporates the most updated information from several reliable medical toxicology resources. Moreover, we have enriched this guide with several valuable charts, forms and antidote tables to aid the frontline health care providers to deal with commonly encountered poisoning cases in a seamless, step wise approach.

We are dedicated to continually improve and update this guide and incorporate more topics on regular basis in order to better meet the needs of the health care providers as well as the public. This guide comes in perfect alignment with our strategic initiatives that are aimed to push the medical toxicology service forward all across the kingdom. We would like to thank all of those who worked hard in order for this valuable document to see the light and are looking forward to achieve more goals and initiatives in the near future.

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PREFACE 2

Medical Toxicology is a medical subspecialty focusing on the diagnosis, management and prevention of poisoning and other adverse health effects due to medications, occupational, environmental toxins, and biological agents. It is necessary to establish evidence based medical source for management of acute intoxicated cases in Saudi Arabia. General Directorate of Poison Control Centers delighted to present 1st edition of Medical Toxicology Guide, which distills the major principles and concepts of medical toxicology practice. It is hoped that the guide will be useful to staff members in medical toxicology practice, as well as targeted personnel from other disciplines, who want to have a strong foundation in medical toxicological concepts and principles.

Care has been taken to confirm the accuracy of the information presented and to describe generally accepted practices. However, application of this information in a particular situation remains the professional responsibility of the practitioner. I invite the readers to send us their suggestions of ways to improve this guide at ***dpccs@moh.gov.sa*** . Finally, I would like to acknowledge all individuals who were involved in this project.

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TOPIC	PAGE

LIST OF CHARTS

LIST OF FORMS

LIST OF ABBREVIATIONS

ABG	Arterial Blood Gases
AC	Activated Charcoal
ACLS	Advanced Cardiac Life Support
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AXR	Abdominal X- Ray
BUN	Blood Urea Nitorgen
CBC	Complete Blood Count
CCB	Calcium Channel Blocker
CNS	Central Nervous System
CO	Carbon Monoxide
CVP	Central Venous Pressure
CVS	Cardiovascular system
CPK	Creatine Phosphokinase
CXR	Chest X- Ray
ECTR	Extracorporeal Therapy
EKG	Electrocardiogram
GCMS	Gas Chromatography Mass Spectrometry
GCS	Glasgow Coma Score
INR	International Normalized Ratio
LFT	Liver Function Tests
MDAC	Multiple Dose Activated Charocal
NAC	N-acetyl Cysteine
NaHCO3	Sodium Bicarbonate
NAPQI	N-acetyl-p-benzoquinoneimine
NSAID	Non-steroidal anti-inflammatory drug
OPIDN	Organophosphate agent-induced delayed neuropathy
PCLS	Pediatric Cardiac Life Support
PTT	Partial Thromboplastin Time
PT	Prothrombin Time
RFT	Renal Function Tests
TCA	Tricyclic Antidepressant

GENERAL TOXICOLOGY

WHAT IS TOXICOLOGY?

Toxicology is "*the science of poisons.*"

More descriptive definition: "*The study of the adverse effects of chemicals or physical agents on living organisms*".

MAJOR PATHOPHYSIOLOGIC TOXIC MECHANISMS:

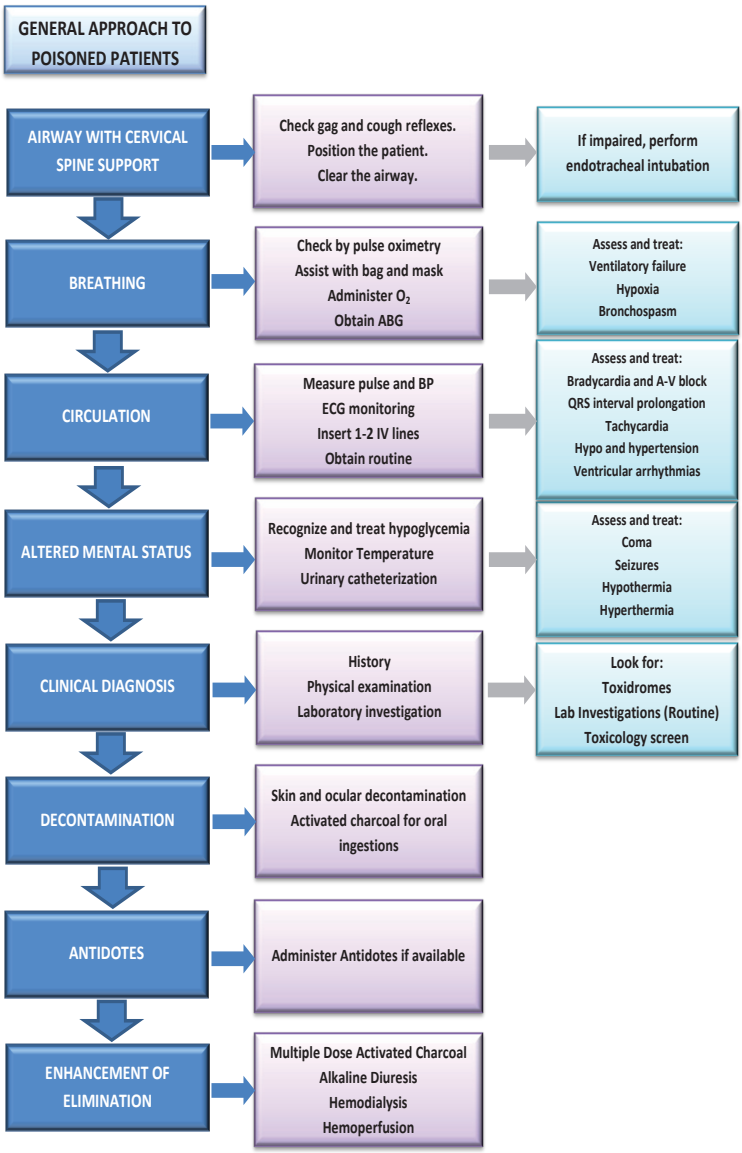
Toxic substances have 9 common major pathophysiologic mechanisms:

1. Substances that produce local tissue damage (corrosives).
2. Toxins that produce damage to the lungs through aspiration (hydrocarbons) or systematically (paraquat).
3. Substances that may stimulate or depress the CNS and produce coma (opioids, sedative-hypnotics) or convulsions (cocaine, amphetamines).
4. Compounds that modulate the autonomic nervous system producing cholinergic effects (organophosphorus and carbamates insecticides) or anticholinergic action.
5. Substances that may affect the heart, producing myocardial dysfunction (tricyclic antidepressants), dysrhythmias (quinidine), hypertension (cocaine, amphetamine), and hypotension (β blockers and calcium channel blockers).
6. Substances that damage the liver (paracetamol) or kidneys (metals).
7. Substances that interfere with the transport or tissue utilization of oxygen (cyanide, hydrogen sulphide and carbon monoxide) resulting in hypoxia.
8. Substances that disturb the acid-base balance such as methanol toxicity which produces metabolic acidosis.
9. Hematological toxicity as seen in warfarin and super-warfarin toxicity.

GENERAL APPROACH TO ACUTELY POISONED PATIENTS

Objectives:

To acquire a systematic approach to the resuscitation, work-up, diagnosis and treatment of acutely poisoned patients.


GENERAL APPROACH TO POISONED PATIENTS
AIRWAY WITH CERVICAL SPINE SUPPORT
Check gag and cough reflexes.
Position the patient.
Clear the airway.
If impaired, perform endotracheal intubation
BREATHING
Check by pulse oximetry
Assist with bag and mask
Administer O_2
Obtain ABG
Assess and treat:
Ventilatory failure
Hypoxia
Bronchospasm
CIRCULATION
Measure pulse and BP
ECG monitoring
Insert 1-2 IV lines
Obtain routine
Assess and treat:
Bradycardia and A-V block
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Hypo and hypertension
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Hemodialysis
Hemoperfusion

GENERAL PRINCIPLES FOR MANAGEMENT OF ACUTE POISONING:

- Treat the patient, not the poison.
- Supportive care is the mainstay of management.
- Patients presenting with acute poisoning must be accurately, and thoroughly assessed, and provided with prompt therapy.
- It is essential to determine if the poisoning:
    - Is life-threatening and is causing deterioration in vital functions.
    - Poses a potential hazard.
    - Is possibly harmless.
- In case of a life-threatening poisoning, emergency treatment begins with the initial rapid assessment and resuscitation.
- While assessing the severity of the poisoning, information regarding the toxic agent (e.g., name, amount, route, duration of exposure, time since exposure and prior treatment received) are necessary.
- It should be borne in mind that often the histories are incorrect concerning the substance, quantity, and even actual exposure. However, early identification of the toxic substance can save time and decrease the risk of toxicity and complications, particularly where a specific antidote could be life-saving or can prevent organ damage. Obtaining the original left over from the suspected toxic agent or its container is more reliable for rapid and positive identification of the poison.
- Call the regional Poison Control Centre for information (800-4428-800 or 937).
- An early collection of biological samples is warranted to establish baseline values for monitoring toxic agents e.g., blood, urine, and other body fluid samples.
- Risk factors such as age, current medications, history of medical/ psychiatric illnesses, and allergy to drugs, drug abuse, and pregnancy should also be considered.
- Patients could present to the ER without symptoms for the following possible reasons:
    1- Exposure to a non-toxic substance (See list of non-toxic substances P. 221).
    2- Ingestion of insufficient amounts of a poison to result in poisoning.
    3- Delayed absorption of the toxic substance (common with belladonna alkaloids, antihistamines, phenothiazines, atropine,

tricyclic anti-depressants and ingestion of toxins while stomach is full (except for fat-soluble poisons).

4- Ingestion of sustained release preparations in which the absorption is delayed and prolonged.

5- Delayed symptoms if only the metabolite of the substance ingested is toxic and not the substance itself (e.g. methanol that is metabolized to formic acid, etc.).

- Carefully record the events and procedures in cases where suicide is suspected.
- Always fill up the history intake and reporting form for poisoned cases.

EMERGENCY EVALUATION AND LIFE-SAVING TREATMENT

- Primary assessment and resuscitation – the ABCDEs.
- Secondary assessment – history, detailed clinical examination and laboratory evaluation (establishing diagnosis).

I- PRIMARYASSESSMENT AND RESUSCITATION – THE ABCDES

- Immediate Stabilization: In infants and children ABC (Airway, Breathing, and Circulation); in adults CAB (Circulation, Airway, and Breathing)

A= AIRWAY with cervical spine control:

Assessment:

- The most prevalent factor contributing to mortality from drug overdose is loss of airway protective reflexes with subsequent airway obstruction by a flaccid tongue, aspiration of gastric contents, or respiratory depression.
- All poisoning patients should be managed as if they have a potentially compromised airway.
- Patients who are awake and talking are likely to have intact airway reflexes, but should be monitored closely, as a deterioration of their condition, can result in rapid loss of airway control.
- In lethargic or obtunded patients, the gag or cough reflexes may be indirect indicators of the patient`s ability to protect the airway. If there is any doubt regarding the patient`s ability to protect his airway, it is best to perform endotracheal intubation.

Treatment:

- Optimize the airway position and clear the airway.
- Perform endotracheal intubation if indicated.

B= BREATHING:

- Assess breathing (respiratory rate, depth, rhythm and sounds). Normal respiratory rate in adults varies from 12-18 breaths / minute. Any respiratory rate >20 or <10/min is abnormal in adults (infants normal respiratory rate is) 25-30/min.
- Ensure adequate ventilation and oxygenation. Quickly obtain bedside pulse oximetry and arterial blood gases.
- If the patient is not breathing or breathing inadequately (O_2 saturation < 90% and pCO_2 > 50 mm Hg), begin ventilation with a bag-valve-mask (BVM) and give 100% O_2.
- If the patient is breathing but O_2 saturation is between 90 - 95 %, supplement with high flow O_2.
- Breathing difficulties are the major cause of morbidity and mortality in poisoned patients.
- Assess and treat ventilatory failure, hypoxia and bronchospasm.

C= CIRCULATION

- Insert IVs ⇒ Draw blood ⇒ Begin IV infusion ⇒ Monitor, pulse, and blood pressure ⇒ CPR if no pulse and ACLS for arrhythmias and shock ⇒ Continuous EKG monitoring.
- Assess and treat Bradycardia and A-V block, QRS interval prolongation, Tachycardia, Hypotension, Hypertension and possible cardiac arrhythmias.

D= DISABILITY (NERVOUS SYSTEM)

- Determine the level of consciousness using the AVPU method:
- A = Alert, V = Responds to verbal stimuli, P = Responds to painful stimuli and U = Unresponsive.
- Continuously assess the level of consciousness.
- Assess pupil size, reactivity and extra ocular movements.
- Check for reflexes and other neurological signs (dystonia, rigidity, and dyskinesia) and rhabdomyolysis.
- Treat seizures promptly with Diazepam (0.1 - 0.2 mg/kg IV slow injection), can repeat q 1-2 hrs as needed. You can use Lorazepam 0.05-0.1mg/kg IV slow injection or Midazolam 0.05-0.1mg/kg IV or IM in place of Diazepam, depending upon the availability. Phenobarbitone (15 mg/kg IV) slowly can be used if convulsions remain uncontrolled with Diazepam.

- Coma or stupor is the most common serious complications in acute poisoning.
- Consider excluding other causes of coma (trauma, meningitis, encephalitis, and CVA)
    1- Maintain the airway, assist ventilation and administer oxygen.
    2- Unless specifically contraindicated within the first 5 minutes of managing a patient with an altered mental status due to an unknown cause, four therapeutic agents should be considered:
        (a) Hypertonic dextrose 0.5–1.0 gm/kg of D50W for an adult, or a more dilute dextrose solution (D10W or D25W) for a child. The dextrose is administered to diagnose and treat or exclude hypoglycemia.
        (b) Thiamine 100 mg IV for an adult (usually unnecessary for a child) to prevent or treat Wernicke`s encephalopathy.
        (c) Titrated naloxone beginning at 0.04 mg IV for an adult or child with suspected opioid-induced respiratory compromise.
        (d) High- flow oxygen (8–10 L/min) to treat hypoxia.
- Monitor core temperature (rectal) and maintain normothermia. Associated hypothermia should be assessed and treated by rewarming (blankets, warm IV fluids, and warm mist inhalation) slowly to prevent rewarming arrhythmias. Do not treat associated bradycardia. Do not give excessive fluids.
- Patients with life-threatening hyperthermia (temperature > 40°C or >104°F), should be treated immediately according to the following step-wise approach:
    1. Maintain the airway, assist ventilation and administer oxygen.
    2. Give glucose containing IV fluids, control seizures, agitation.
    3. Start external cooling with tepid (lukewarm) water sponging and fanning, the aim is to bring the temperature to 38.6°C.
    4. Exclude other causes of hyperthermia (drug withdrawal, heat stroke, thyrotoxicosis, meningitis, encephalitis, or other systemic infections).
    5. For malignant hyperthermia, administer Dantrolene (1-10 mg/kg IV).
    6. In case of anticholinergic poisoning, antidote treatment may reduce hyperthermia.

E = EXPOSURE WITH ENVIRONMENTAL CONTROL

- The poisoned patient should be completely undressed and examined thoroughly, particularly for signs of trauma, burns, puncture marks, rash, petechiae, etc. removal of clothing is also warranted for necessary skin decontamination.
- Assess and treat anaphylaxis.
- Assess and treat rhabdomyolysis by:
    1- Obtaining serum creatinine and creatine phosphokinase (CPK) levels.
    2- Administering IV fluids; maintain urine flow to 3-5 ml/kg/hr.
    3- Mannitol 0.5 gm/kg IV can be considered in patients with oliguria.
    4- Alkalinize urine by adding 100 mEq of sodium bicarbonate to each liter of D5W.
- Maintain airway and ventilation in cases presenting with dystonia, dyskinesia, and rigidity.
- For dystonia, administer Diphenhydramine 0.5-1mg/kg IM.
- For dyskinesia, administer Diazepam, if uncontrolled, search for the cause (spider bite/malignant hyperthermia or Neuroleptic syndrome), and treat accordingly.

II- SECONDARY ASSESSMENT – DIAGNOSIS OF POISONING

- After the primary assessment and resuscitation, the patient should undergo a secondary assessment. as follows:
    1- A careful history.
    2- A detailed clinical examination.
    3- Clinical laboratory tests.

History:

- Often: Incomplete, unreliable or unobtainable.
- Sources: Patient, friends, family, empty pill containers.
- Inquire about all the drugs taken, including prescribed as well as, over the counter medications, herbs, and vitamins.
- Ask family members or friends, about any prescription or over the counter medication known to be used by the patient or others in the house.
- Obtain any available drugs for later testing.
- Ask about the dose, time, and route of administration.

- Inquire about liver, renal, cardiac and pulmonary disease, concurrent medications, previous overdoses, substance abuse and smoking.
- ***History should be directed towards identifying the following*:**
    1- Type of poison (chemical, drug, insect bite/sting, plant).
    2- Amount / quantity.
    3- Route of exposure.
    4- Time since exposure.
    5- Reason for exposure.
    6- Time of onset of symptoms in relation to exposure.
    7- Treatment received prior to arrival to hospital.

Physical examination:

- A physical examination should be performed rapidly, but thoroughly. Key elements of the directed examination include an evaluation of the mental status, pupil size and reactivity, skin moisture, bowel sounds, and bladder size (urinary retention). Characteristic breath or skin odors may help identify the etiology of coma.
- *The* detailed *clinical examination is essential to diagnose poisoning and should include the following:*
    1) Reassessment of vital functions. Carefully examine chest for respiratory and cardiovascular functions.
    2) Assess neurological status. The level of consciousness is usually assessed in the secondary assessment by using the Glasgow Coma Score (GCS). A GCS of 8 or less strongly indicates that the patient will not be capable of adequately protecting his airway and may require endotracheal intubation. Patients who are drowsy or stuporous will often not require intubation provided they are nursed on their side and continually assessed, e.g., in alcohol or benzodiazepine over dose.
    3) Assess psychosis, agitation and changes to the cognitive function.
    4) Assess for any other neurological changes (e.g., reflexes, motor dysfunction, extra ocular movements, etc).
    5) Examine carefully pupil-size, reaction, nystagmus, and fundus.

6) Examine skin for temperature, dry/moist, colour (pale, cyanosed), bleeding, rash, piloerection, bullae, burn injury, sting / bite marks, and needle tracks.
7) Examine gastrointestinal system starting from the mouth (oral mucosa burn, breath odor) abdominal tenderness, bowel sounds, abdominal distension, and check the stools.
8) Examine genitourinary system for distension of bladder, and check for urine output and color of urine.
9) Record the body weight of the patient.

TOXIDROMES

- They are characteristic clinical signs and symptoms suggesting a specific drug class.
- They need high index of suspicion, history and good physical examination.
- Common Toxidromes include: Sympathomimetic – cholinergic – anticholinergic – opiate - sedative hypnotic - withdrawal (alcohol, benzodiazepines and opiates).

Sympathomimetic Toxidrome

Mental status	Pupils	Vital signs	Other manifestations	Examples of toxic agents
Hyperalert, agitation, hallucinations, paranoia	Mydriasis	Hyperthermia, tachycardia, hypertension, wide pulse pressure, tachypnea, hyperpnea	Diaphoresis, tremors, hyper-reflexia, seizures	Cocaine, amphetamines, cathinones, ephedrine, pseudoephedrine, caffeine, phenylpropanolamine, theophylline,

Anticholinergic Toxidrome

Mental status	Pupils	Vital signs	Other manifestations	Examples of toxic agents
Hypervigilance, agitation, hallucinations, delirium with mumbling speech, coma	Mydriasis	Hyperthermia, tachycardia, hypertension, tachypnea	Dry flushed skin, dry mucous membranes, decreased bowel sounds, urine retention, myoclonus, choreoathetosis, picking behavior, seizures(rare)	Antihistamines, tricyclic antidepressants cyclobenzaprine, orphenadrine, antiparkinson agents, antispasmodics phenothiazines, atropine, scopolamine, belladonna alkaloids (eg, Jimson Weed)

Cholinergic Toxidrome

Mental status	Pupils	Vital signs	Other manifestations	Examples of toxic agents
Confusion, coma	Miosis	Bradycardia, hypertension or hypotension, tachypnea or bradypnea	Salivation, urinary and fecal incontinence, diarrhea, emesis, diaphoresis, lacrimation, GI cramps, bronchoconstriction, muscle fasciculations, seizures, and weakness	Organophosphate and carbamate insecticides, nerve agents, nicotine, pilocarpine, physostigmine, edrophonium, bethanechol, urecholine

Cholinergic Toxidrome

Mental status	Pupils	Vital signs	Other manifestations	Examples of toxic agents
Confusion, coma	Miosis	Bradycardia, hypertension or hypotension, tachypnea or bradypnea	Salivation, urinary and fecal incontinence, diarrhea, emesis, diaphoresis, lacrimation, GI cramps, bronchoconstriction, muscle fasciculations, seizures and weakness	Organophosphate and carbamate insecticides, nerve agents, nicotine, pilocarpine, physostigmine, edrophonium, bethanechol, urecholine

Opioid Toxidrome

Mental status	Pupils	Vital signs	Other manifestations	Examples of toxic agents
CNS depression, coma	Miosis	Hypothermia, bradycardia, hypotension, apnea & bradypnea	Hyporeflexia, pulmonary edema, needle marks	Opioids (eg, heroin, morphine, methadone, oxycodone, hydromorphone, diphenoxylate

Sedative-hypnotic Toxidrome

Mental status	Pupils	Vital signs	Other manifestations	Examples of toxic agents
CNS depression, confusion, stupor, coma	Miosis (usually)	Hypothermia bradycardia, hypotension, apnea & bradypnea	Hyporeflexia	Benzodiazepines, barbiturates, carisoprodol, meprobamate, glutethimide, alcohols, zolpidem

Withdrawal Toxidrome

Mental status	Pupils	Vital signs	Other manifestations	Examples of toxic agents
Alter mental status	Mydriasis	Hyperthermia, tachycardia, hypertension & hyperventilation	tremors, hyperreflexia, seizures, nausea, vomiting	Withdrawal (EtOH, BDZ, opiates)

Serotonin Toxidrome

Mental status	Pupils	Vital signs	Other manifestations	Examples of toxic agents
Confusion, agitation, coma	Mydriasis	Hyperthermia, tachycardia, hypertension & tachypnea	Tremors, myoclonus, hyperreflexia, clonus, diaphoresis, flushing, trismus, rigidity, diarrhea	MAOIs alone or with: SSRIs, meperidine, dextromethorphan, TCAs & L-tryptophan

Hallucinogens Toxidrome				
Mental status	Pupils	Vital signs	Other manifestations	Examples of toxic agents
Hallucinations, perceptual distortions, depersonalization, synesthesia, agitation	Mydriasis (usually)	Hyperthermia, tachycardia, hypertension & tachypnea	Nystagmus	Phencyclidine, LSD, mescaline, psilocybin, designer amphetamines (e.g., MDMA ["Ecstasy"])

Comparison between anticholinergic and sympathomimetic Toxidromes		
	Anticholinergic	**Sympathomimetic**
Skin	Dry	Diaphoresis
Bowel sound	Inhibited	Hyperactive
Urine retention	Present	Absent
Pupil	Dilated fixed	Dilated reactive

INVESTIGATIONS

Routine:

- Random blood glucose (RBS), electrolytes (Na, K, Cl, Ca, Ph), renal function tests (RFT) (BUN, Creatinine), liver function tests (LFT) (ALT AST, Bilirubin, ALP), ABGs, and CBC.
- General laboratory tests are more useful than toxicology screens.

Specific:

- Are indicated in following cases:
  1) Intentional ingestions
  2) Unknown substance.
  3) The substance can potentially produce moderate to severe toxicity.
- Blood tests in which the specific drug levels are of clinical significance, commonly requested and should be readily available: Acetaminophen, Salicylates, Digoxin, Carbamazepine, Phenobarbitone, Phenytoin, Valproate, Theophylline, Iron, and Lithium.
- Qualitative Urine Assays in which the substance is commonly screened for (positive or negative): Amphetamines, Barbiturates, Cocaine, Opiates, Propoxyphene, Phencyclidine, Tricyclic antidepressants, Sedative-Hypnotics, and Cannabis.
- Toxicology screen is used for confirmatory purposes and does not modify the management of the patient.

Additional Tests:

- Electrocardiogram (EKG) for TCA or other cardiotoxic drugs, arrhythmias and ischemia.

Radiological Tests:

- Chest X-ray (CXR) for aspiration pneumonia, non-cardiogenic pulmonary edema (NCPE).
- Abdominal X-ray (AXR) is useful in screening for ingestions of radio-opaque materials.
- Radiodense substances that may be visible on AXR.
- Chloral hydrate, heavy metals, Iron, Phenothiazines, enteric coated preparations, sustained release preparations and drug packets.

DECONTAMINATION

Surface Decontamination:

Skin:

Indications: In poisoning with corrosives, hydrocarbons and toxins rapidly absorbed through the skin e.g. organophosphates.

Method:

- Be careful not to expose yourself or other care providers to potentially contaminated substances and wear protective gear.
- Remove contaminated clothing and flush exposed areas with copious running water or saline.

Eyes:

Indications: In corrosives and hydrocarbons and chemical irritants.

Method: Act quickly to prevent serious damage to the cornea.

1. Flush exposed eye with copious tap water or saline.
2. If available, instill local anesthetic drops first to facilitate eye irrigation.
3. Remove the victim's contact lenses.
4. Position the victim in the supine position under a tap or use intravenous tubing to direct the stream of water.
5. Do not instill any neutralizing solution.
6. After completing irrigation, check the conjunctival and corneal surface. Patients with serious injures should be referred to the ophthalmologist immediately.

Inhalation Decontamination:

Indications: Injury to the respiratory system is often caused by irritant gases and fumes.

Method:

- Be careful not to expose yourself or other care providers to potentially contaminated substances without adequate respiratory protection.
- Remove the victims from the area of exposure and give supplemental O_2 and assess ventilation if necessary. Observe closely for evidence of upper respiratory tract oedema.

- Observe for early signs and symptoms) of late onset non-cardiogenic pulmonary oedema (e.g., tachypnea, dyspnea, and hypoxia).

Gastrointestinal Decontamination:

Indications:

- The decision to perform GI decontamination is based upon:
  1. The specific poisons ingested.
  2. Time from ingestion to presentation at the ER.
  3. Presenting symptoms.
  4. Anticipated severity of poisoning.
- GI decontamination is most likely to be of benefit if patients present with the following:
  1. Recent ingestion of toxins (usually within one to two hours).
  2. Ingestion of a poison and an amount suspected to cause toxicity.
  3. No clinical signs (e.g., somnolence) that render decontamination dangerous.
- GI decontamination should not be carried out if the agent and amount ingested are nontoxic, if the agent is considered fully absorbed due to delayed presentation, or if the toxin is not responsive to decontamination.

METHODS OF GIT DECONTAMINATION:

1. Single dose of activated charcoal (AC):

Activated charcoal is a fine, black, odorless powder. It is made from combustion of organic material & treated to increase surface area.

A) Action: Reduces the systemic absorption of many drugs by adsorption of drugs to the surface of charcoal. It also acts to enhance elimination by disrupting substantial enterohepatic recirculation.

B) Dose: 1-2 gm/kg in adults and 0.5–1 gm/kg in children.

C) Complications: Adsorb any other oral antidotes administered. Gastrointestinal side effects include fullness, abdominal pain,

nausea, vomiting, constipation, GI obstruction, diarrhea and aspiration.

D) Contraindications:
   1. Coma or convulsions
   2. Absence of bowel sounds
   3. Perforation or Intestinal obstruction – Need for endoscopy (Caustics)
   4. Late presentation - Toxins poorly adsorbed by AC.

E) Agents for which activated charcoal is not effective (does not adsorb the poison):
   1. Heavy metals: Arsenic, Lead, Mercury, Iron, Zinc and Cadmium.
   2. Inorganic ions: Lithium, Sodium, Calcium, Potassium, Magnesium, Fluoride, and Iodide.
   3. Corrosives: Acids and Alkalis.
   4. Hydrocarbons: Alkanes, Alkenes, Alkyl halides, and Aromatic hydrocarbons.
   5. Alcohols: Acetone, Ethanol, Ethylene glycol, Isopropanol and Methanol.
   6. Essential oils.

2- Multiple-Dose Activated Charcoal (MDAC):

A) Indications:
   - Very large ingestions of toxic substance.
   - Drugs remaining in the GIT as sustained release and enteric coated preparations.
   - Drugs forming concretions e.g. salicylates and phenobarbital.
   - Drugs slowing GIT motility e.g. anticholinergic and carbamazepine.
   - Interruption of enterohepatic recirculation as in digoxin toxicity.
   - Facilitation of transluminal diffusion from the body into the bowel lumen (“Gut dialysis”) as in theophylline.

B) Dose:

- When the decision has been performed to use multiple-dose activated charcoal, a repeat dose may be given every 2 to 6 hours. A uniform dose has not been established. Suggested regimens involve:
  - 0.5 g/kg every 2-4 hours.
  - 20 g every 2 hours, 40 g every 4 hours or 60 g every 6 hours.
- The duration of treatment has not been established. A typical approach is to continue it for 24 to 48 hours.
- Continuous nasogastric instillation of activated charcoal, 0.25-0.5 g/kg/h, has been recommended to decrease the incidence of emesis.
- When the first dose of activated charcoal is associated with cathartic, subsequent doses of activated charcoal should not be administrated with a cathartic because of the high risk incidence of fluid and electrolyte disturbances. Note that some active charcoal preparations already contain a cathartic.

3- Gastric Lavage:

- To date, the evidence to support a beneficial role for gastric lavage in reducing the severity, recovery time or improving outcome for poisoned patients is weak, even if started within 60 minutes. According to the American Academy of Clinical Toxicology (AACT) and the European Association of Poison Control Centers and Clinical Toxicologists (EAPCCT), most of the studies that were performed to study the efficacy of gastric lavage did NOT provide evidence to support its use and the studies that reported benefit from gastric lavage had significant flaws that rendered them weak. We currently do NOT recommend the routine use of gastric lavage if at all, as there are no clear guidelines to indicate the conditions where it is appropriate to use it (2). In the rare event that an attending physician is considering to perform gastric lavage for a particular patient, we advise that he/she would consult a medical toxicologist prior to performing the procedure.

4- Whole Bowel Irrigation (WBI):

- Consists of using the surgical bowel-cleansing solution polyethylene glycol in a balanced, isotonic electrolyte salt solution (movicol, etc.).
  A) Action: Whole-bowel irrigation is a method of flushing the gastrointestinal tract in an attempt to reduce further absorption of drugs.
  B) Procedure:
     - The solution is administered as 0.5L/hr in children < 5 years & 1-2 L/hr for adults.
     - It is administered by nasogastric tube or orally.
     - The end-point is recovery, and return of the drug to therapeutic levels.
  C) Indications:
     - Substances poorly adsorbed by AC (iron, lead). Sustained-release or Enteric coated tablets.
     - In cases of body packers (cocaine, heroin).
  D) Contraindications:
     - Extensive hematemesis, paralytic ileus, bowel obstruction and, perforation or peritonitis.
  E) Complications:
     - Nausea & vomiting, aspiration and, decreasing the effectiveness of activated charcoal.

5- Surgery & Endoscopy:

Surgery and endoscopy are occasionally indicated for decontamination of poisoned patients if the other methods failed. Generally, this method is used for body packers (cocaine, heroin) and bezoars formation in drugs like, salicylate, iron, and barium.

ENHANCEMENT OF ELIMINATION

Indications for enhanced elimination:

1. Patients who fail to respond adequately to full supportive care.
2. Patients in whom the normal route of elimination of the drug is impaired.
3. Patients in whom the amount of drug absorbed is high or its concentration is high enough in the serum to indicate that serious morbidity or mortality are eminent.
4. Patients with concurrent disease or in an age group (very young or old) associated with increased risk of morbidity or mortality from the overdose.
5. Patients with concomitant electrolyte imbalances that could be addressed by hemodialysis as lactic acidosis associated with metformin toxicity.

- ***Certain methods are applied to enhance excretion of the poison from the blood after being absorbed. They include the following:***

I. Multiple doses Activated Charcoal (MDAC) previously discussed.

II. Manipulation of Urine pH:

Mechanism:

It is the change of the urine pH in order to present the drug for the kidney in its ionized form. Drugs can be weak acids or bases. If they are rendered ionized, they are not reabsorbed easily by the renal tubules, so they are readily excreted.

Alkalization of urine:

Drugs likely to respond to urinary alkalinization are usually characterized by:

1. Being predominantly eliminated unchanged by the kidney.
2. Distributed primarily in the extracellular fluid compartment.
3. Minimally protein-bound and weak acids such as, salicylates and phenobarbitone, which have greater ionization and better excretion at urine pH of 7.5 - 8.

1) Indications:

Salicylates, phenobarbital, chlorpropamide, formate, diflunisal, fluoride, methotrexate, the herbicide chlorphenoxyacetic acid and poisons producing hemolysis and rhabdomyolysis.

2) Methodology:

Add 150 mEq (3 ampoules of 8.4%) of NaHCO3 to 1 liter of D5W to provide an isotonic solution and 20-40 mEq of potassium chloride/ liter are added as needed to maintain normokalemia. Administer 10-20 mL/kg initially as a bolus then infuse at 2-3 mL/kg/hr. It should be infused at a rate sufficient to induce a urine output of 2-3 mL/kg/hr. Urine pH should be frequently checked every 1-2 hrs.

3) Precautions:

- Keep urinary pH at 7.5-8.
- Keep urine output at 3-5 ml/Kg/hr closely observing input / output chart.
- Normal renal functions should be ascertained before the start of diuresis.
- Blood pH and electrolytes should be monitored, especially serum K as the infusion of NaHCO3 may lead to hypokalemia.
- Auscultate the lung bases for the possibility of pulmonary oedema.

4) Complications:

- Acid-base and electrolyte imbalance.
- Fluid overload with pulmonary and cerebral edema.

III. Dialysis (Extracorporeal Elimination)

- The principle of dialysis is to allow blood to circulate in contact with a semi-permeable membrane to remove substances from the blood via a concentration gradient. Dialysis is beneficial when renal functions become impaired.
- Dialyzable drugs should have the following characteristics:
  - A) Have a small volume of distribution (<1L/kg).
  - B) Have low protein binding.
  - C) Have small molecular weight < 500 Daltons.
  - D) High water solubility.
  - E) Low endogenous clearance (< 4 ml/min/kg).
- Examples of dialyzable drugs: Alcohols, Phenobarbital, Lithium, Salicylates, and Theophylline.

A. Hemodialysis

In addition to removal of toxins, it can correct acid-base and electrolyte disturbances, and extracellular fluid volume overload.

Complications: Hypotension, muscle cramps, elimination of therapeutically administered drugs, bleeding tendency (due to heparin), deep venous thrombosis (DVT), air embolism, electrolyte imbalance, infection, and hepatitis.

Contraindications: Non-dialyzable toxic agents, patients with coagulopathy, patients with uncorrected hypotension.

B. Peritoneal dialysis

Peritoneal dialysis is a relatively simple method to enhance xenobiotic elimination. It is too slow to be clinically useful. Peritoneal dialysis is therefore, never the method of choice unless hemodialysis and hemoperfusion are unavailable.

Complications: Intra-abdominal bleeding, perforation of abdominal organs, peritonitis, dehydration or over-hydration.

Contraindications: Pregnancy, abdominal hernia or respiratory distress.

C- Hemoperfusion:

This method allows blood derived from the radial artery to pass through a cartridge coated with activated charcoal to adsorb poisons existing in the plasma. It can be done for toxins with high protein binding, or for those having big molecular weight, and also in lipid-soluble drug. The poison must be adsorbed to charcoal.

Complications*:* Trapping of white blood cells and platelets causing a reduction in the platelet count, reduction in (serum calcium, glucose), hypotension, adsorption of therapeutically administered drugs.

ADMISSION CRITERIA FOR A POISONED PATIENT

ADMISSION OF ASYMPTOMATIC PATIENTS:

Any individual presenting with ingestion of a toxic substance must be admitted under observation for 4 hrs after which he/she can be discharged if still asymptomatic except in the following conditions:

1. Ingestion of a poison with a delayed onset of action.
2. Intake of sustained release or enteric-coated preparations.
3. Toxic level of the poison in the blood analysis.
4. Intake of a substance that is known to be highly toxic.

ADMISSION OF SYMPTOMATIC PATIENTS:

Patients that are symptomatic but are stable e.g., normal vital signs, normal acid base balance, electrolytes, normal consciousness level, and the level of the drug/poison is not highly elevated, can be admitted to the inpatient unit.

INTENSIVE CARE UNIT (ICU) ADMISSION:

Patients presenting with acute poisoning are often admitted to the ICU, mainly for close observation and monitoring. Intensive care units allow healthcare providers the best opportunity to minimize the risk of morbidity and mortality. Patients should be admitted to the ICU based upon the following:

1) Severity of illness:

- The Acute Physiology and Chronic Health Evaluation (APACHE II/III), the Mortality Probability Model (MPM II), and the Pediatric Risk of Mortality (PRISM II/III) are widely utilized and generally accepted severity-of-illness models that utilize physiologic parameters and other factors in order to estimate risks and predict outcomes in critically ill patients.
- The Glasgow Coma Score (GCS) is a commonly used bedside tool to quickly assess the severity of physiologic derangement and altered neurologic status.

2) Drug-induced end-organ toxicity:

- The presence of certain signs, symptoms, or abnormal diagnostic tests requires ICU observation or intervention. Examples of clinical conditions that require ICU care:

A. *Vital signs*: Profound alteration in any vital sign, including temperature.
B. *Central nervous system (CNS)*: Delirium, coma, convulsion and status epilepticus.
C. *Respiratory*: Dyspnea, persistent hypoventilation, acute lung injury, and hypoxia.
D. *Cardiac*: Dysrhythmias, hypotension, hypertension, and tissue ischemia.
E. *Hepatic*: Liver failure.
F. *Renal/metabolic*: Severe metabolic acidosis and electrolyte disturbances.

3) Extremes of age:

- Such as infants and elderly patients who have chronic medical problems.

4) Physiologic monitoring and specialized treatment:

- The ICU setting offers highly skilled staff. It also provides a nurse-to-patient ratio that allows for frequent or continuous monitoring of basic physiologic parameters and invasive monitoring.
- Most critically ill poisoned patients that have acute reversible conditions requiring supportive care measures (e.g., ventilator support, vasopressor support and close monitoring).
- Most often, supportive care measures improve the outcome of critically ill, poisoned patients more than antidotes and specialized treatments.

CRITERIA FOR DISCHARGING POISONED PATIENTS

- Poisoned patients that were admitted as a result of positive clinical manifestations can be discharged after a period of observation not less than 24 hrs after normalizing all abnormal clinical signs, symptoms and laboratory analysis.
- Patients in which delayed complications are expected, follow up appointments are warranted for early detection and possible intervention to control these complications.

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SYSTEMIC TOXICITY

ANALGESICS & ANTIINFLAMMATORY DRUGS

ACETAMINOPHEN POISONING

(PARACETAMOL POISONING)

INTRODUCTION:

- Acetaminophen [APAP] poisoning is one the most prevalent causes of medication-related poisoning and death worldwide. Serious poisoning from acetaminophen can result following a single acute ingestion or through the repeated ingestion of supratherapeutic doses.
- **Toxic dose:** (150-200 mg/kg or a total dose of 6-7 gm in adults), check increased frequency of dosing, check time of ingestion and time delay.
- **Epidemiology:**

  Common: Intentional overdose is common

  Mild: Toxicity is typically mild if the patient is treated early

  Unusual: Death is unusual, developing in patients who present after 24 hours or in whom treatment is mistakenly withheld.

  Rare: "Chronic" acetaminophen toxicity may result from repetitive, supra-therapeutic dosing; such poisonings are usually unintentional and occur in adults with acute, persistent pain syndromes or in persistently febrile infants. Adults who ingest greater than 4 g/day for more than 1 day, and infants less than 2 years of age who are given more than 150 mg/kg/day for more than 1 day may be at increased risk.

MECHANISM OF TOXICITY:

- Approximately 90% of acetaminophen normally undergoes hepatic conjugation with glucuronide and sulfate to form inactive metabolites, which are eliminated in the urine
- A small fraction of unchanged acetaminophen (< 5%) and other minor metabolites reach the urine but are not thought to be clinically relevant.
- The remaining fraction, usually ranging from 5-15%, is oxidized by the cytochrome-P 450 system (CYP2E1) resulting in the formation N-acetyl-p-benzoquinoneimine (NAPQI).

- Glutathione quickly combines with NAPQI. The resulting complex is then converted to nontoxic cysteine or mercaptate conjugates, which are eliminated via the kidneys.
- In overdose, the usual metabolic pathways are over burdened, and acetaminophen is metabolized by CYP2E1 to the reactive metabolite (NAPQI). Glutathione is able to detoxify NAPQI via conjugation, but when hepatic glutathione stores become depleted, the metabolite alternatively binds to macromolecules in the hepatocyte resulting in cell death and hepatic necrosis.

CLINICAL MANIFESTATIONS:

- **Stage I** (up to 24 hrs. after overdose): Patients are asymptomatic or have nonspecific clinical findings (e.g., nausea, vomiting, and malaise). Liver functions are normal at this stage.
- **Stage II** (24-72 hrs. after overdose): Right upper quadrant pain, elevation in liver enzymes, prothrombin time (PT) and international normalized ratio (INR) and in severe cases, evidence of nephrotoxicity (elevated BUN, creatinine, oliguria) and/or pancreatitis (elevated serum amylase and lipase).
- **Stage III** (72-96 hrs.): Evidence of liver failure (jaundice, coagulopathy, encephalopathy) and in severe cases acute renal failure, metabolic acidosis and multi-organ failure. Death most commonly occurs in this stage.
- **Stage IV** (4-14 days) recovery phase: Hepatic regeneration, which generally takes several days to a few weeks, becomes complete in survivors.

DIFFERENTIAL DIAGNOSIS:

- Toxicologic: Carbon tetrachloride, hepatotoxic mushrooms, halothane, idiosyncratic drug reactions, pennyroyal oil, and iron.
- Non-Toxicologic: Viral hepatitis A, B, and C, Epstein-Barr virus, cytomegalovirus, varicella), inborn errors of metabolism, hepatobiliary disease, and reye syndrome.

INVESTIGATIONS:

- **Routine:**

1) Monitor serum glucose.
2) Serum electrolytes, ALT, AST, PT, bilirubin, albumin, BUN, creatinine.
3) ABG.

4) EKG.

5) Salicylate level.

6) Pregnancy test in all women of childbearing age.

- The first AST serves as a screen to detect preexistent hepatic disease.
- Measuring the ALT and INR every 12 hrs for any patient who develops ALT elevation.
- Elevated ALT and AST and prolonged PT, bilirubin, glucose, and alkaline phosphatase, indicate the degree of liver failure.

- **Specific:**
  - Paracetamol serum level at 4 hrs post-ingestion (see nomogram).
  - Apply the level on the nomogram in all cases except in chronic ingestion, use of sustained release tablets, alcoholic or hepatotoxic medications (liver toxicity line would be much lower).

ADMISSION CRITERIA:

- Patients who require treatment with N-acetylcysteine are generally admitted to the hospital, although selected patients (presenting early with no evidence of liver injury) may be treated with acetyl cysteine and managed in an emergency department observation unit. Patients with acute liver failure should be admitted to the ICU and may require transfer to a facility with liver transplantation service.

TREATMENT:

- **Stabilization:**
  - Airway, breathing, and circulation (ABC) should be evaluated and stabilized as necessary if the patient came in stage II or III.
- **Decontamination**:
  - Preferably within 1hr of ingestion, give activated charcoal up to 4 hrs post ingestion except in slow release preparations you can give charcoal after 4 hrs (Administer NAC by IV route if indicated).
- **Antidote:**

NAC (N-Acetyl cysteine) start early when indicated.

- Indications for NAC therapy include:

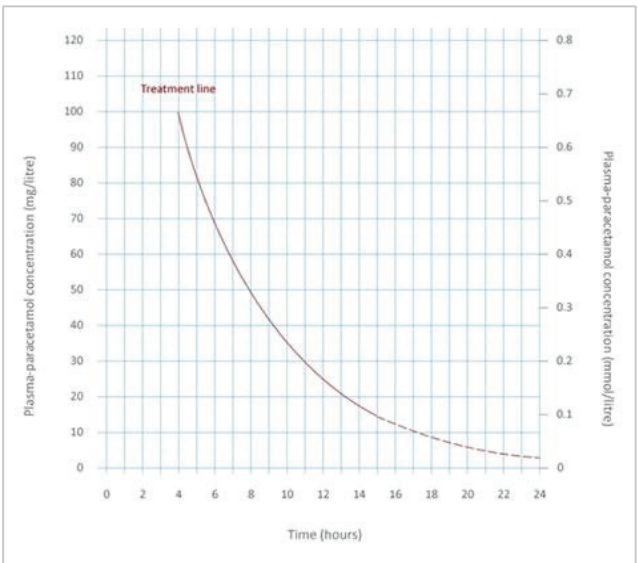
1. Serum acetaminophen concentration drawn at 4 hrs or more following acute ingestion of an immediate-release

preparation is above the "treatment" line of the treatment nomogram for acetaminophen poisoning.

2. A suspected single ingestion of greater than 150 mg/kg (7.5 g total dose regardless of weight) in a patient for whom the serum acetaminophen concentration will not be available until more than eight hrs from the time of the ingestion.
3. Patients with an unknown time of ingestion and a serum acetaminophen concentration of >10 µg/mL (66 µmol/L).
4. Patients with a history of APAP ingestion and evidence of any liver injury.
5. Patients with delayed presentation (>24 hrs after intake and a history of excessive acetaminophen ingestion) with laboratory evidence of liver injury (ranging from mildly elevated aminotransferases to fulminant hepatic failure).

- **The updated treatment nomogram:**

1. All patients with serum acetaminophen level on or > 100 µg/mL at 4 hrs and 15 µg/mL at 15 hrs after ingestion should receive N-acetyl cysteine (Parvolex) based on the new treatment nomogram, wether the risk factors for hepatotoxicity are present or not.
2. If the timing of paracetamol ingestion is unknown, including when ingestion has occurred over an extended period of one hour or more 'staggered overdose', N-acetylcysteine should always be administered without delay (the nomogram should not be used).
3. Administer the initial dose of N-acetyl cysteine as an infusion over 60 minutes to minimize the risk of common dose-related adverse reactions.
4. Hypersensitivity is not a contraindication to treatment with N-acetyl cysteine.



New treatment nomogram for acute acetaminophen overdose

- **Dose and route of administration:**
  - IV administration of NAC is favored for patients who present acutely following ingestion and have any of the following:
    1. Vomiting.
    2. Pregnancy.
    3. Contraindications to oral administration (i.e., pancreatitis, bowel ileus or obstruction, bowel injury).
    4. Patients who refuse oral administration.
    5. Patients with evidence of hepatic failure.
  - IV NAC 20 hrs course: Loading dose 150 mg/kg in 200ml of D5W (for adults) over 1hr followed by 50 mg/kg in 500ml of D5W (for adults) over 4 hrs followed by 100 mg/kg in 1000 ml of D5W (for adults) over 16 hrs. Beware of anaphylactic reaction (bronchospasm, hypotension, wheals, and laryngeal edema). Give adrenaline 0.5 ml SC and IV steroids.
  - IV NAC 48 hrs course: Loading dose 140 mg/kg followed by 70 mg/kg over 4 hrs for 12 doses or 72 hrs course = 17 doses

(superior to the 20hr course when started 16-24 hrs post ingestion).

- Oral NAC: Loading dose 140 mg/kg followed by 70 mg/kg/4 hrs for 17 doses.
- N- Acetyl Cysteine: Preliminary evidence indicates that the antidote, N-acetylcysteine (NAC), crosses the placenta and should be administered to a pregnant woman with the same indications as patients who are not pregnant. An infant born to a mother with acetaminophen toxicity should receive a 48-hour course of intravenous NAC.

- **Extracorporeal treatment (ECTR) (hemodialysis):**
  - Effectively removes acetaminophen from the blood.
  - **Indications***:*
  - ECTR is recommended in the following:
    1. If the APAP is > 1000 µg/mL (6620 µmol/L) and NAC was NOT administered.
    2. In cases presenting with altered mental status, metabolic acidosis, with an elevated lactate, and an APAP is > 700 µg/mL (4630 µmol/L) and NAC is NOT administered.
    3. In cases with an altered mental status, metabolic acidosis, an elevated lactate, and an APAP is more than 900 µg/mL (5960 µmol/L) even if NAC is administered.
  - **Choice of ECTR:**
    - Intermittent hemodialysis is the preferred ECTR in patients with APAP poisoning.
  - **Cessation of ECTR:**
    - ECTR is recommended until sustained clinical improvement is apparent.

NB: NAC therapy should be continued during ECTR at an increased rate.

- **Supportive treatment:**
  1. Antiemetics (metoclopramide or ondansterone).
  2. Monitor and treat hypoglycemia of liver failure. Vitamin K may improve coagulopathy.
- **Indications for Liver Transplantation:**

King's *College Hospital criteria for liver transplantation in paracetamol-induced acute liver failure*: If arterial pH <7.3 or

arterial lactate >3.0 mmol/L after adequate fluid resuscitation.

OR if all three of the following occur in 24-hour period:

1- Creatinine >300 µmol/L.

2- PT >100 seconds (INR >6.5).

3- Grade III/IV encephalopathy.

NB: Some sources recommend measuring serum acetaminophen, international normalized ratio (INR), serum bicarbonate, and serum creatinine after completion of treatment and resuming treatment if any value is abnormal.

- **Chronic acetaminophen toxicity (Repeated Ingestions):**

In children < 6 years of age:

- 200 mg/kg or more over a period of 8-24 hours,
- 150 mg/kg or more per day for 2days.
- 100 mg/kg or more per day for 3 days or more.

Patients > 6 years of age:

- 10 gm or 200 mg/kg (whichever is less) over 24-hour period.
- 6 gm or 150 mg/kg (whichever is less) per day for 2 days or longer.

- **Important Tips**
  - Nonspecific symptoms: nausea, vomiting, abdominal pain (Could be mixed wirh viral syndrome)
  - Diagnosis is dependent on the history. Laboratory analysis (Liver enzymes) may be helpful.
  - Serum concentration does not correlate with toxicity.

Indications for NAC in Chronic Toxicity:

- Elevated AST or ALT (should be monitored for 36 hours after the last ingested dose)
- Paracetamol level > 10 µg/mL
- Symptomatic patients with normal ALT and AST

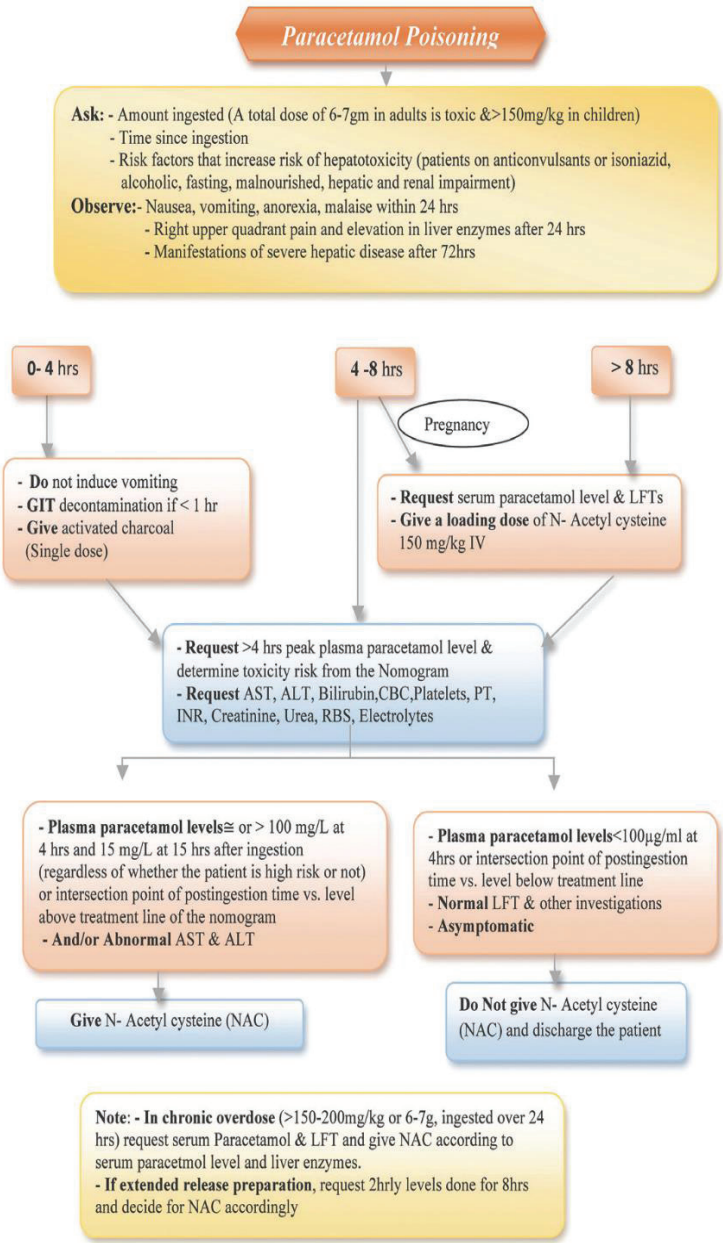
- **Discharging Criteria:**
  - From the emergency department: "Patients may be discharged if":
    - The time of ingestion is certain.
    - The serum acetaminophen level is below the possible toxicity level.

- A psychiatric evaluation has been performed.
- From the hospital: "Patients may be discharged after a full course of NAC, if":
  - Liver and renal function tests are normal or improving.
  - After a psychiatric evaluation, if needed.

- **Patient Educations**
  - Dangers of over counter medications:
    - The health-care professional should educate patients on the potential dangers of over-the-counter medications.
  - Simultaneous usage of acetaminophen preparations:
    - Patients should be cautioned that simultaneous use of more than one acetaminophen product may lead to inadvertent overdose.
  - Substitution of acetaminophen preparations:
    - Substitution of inappropriate formulation (e.g., use of an adult acetaminophen suppository in a child instead of a pediatric one) may result in toxicity.

COMMON PITFALLS:

- **Evaluation:**
  - Failure to determine the accurate time of ingestion.
  - Failure to consider the possible effects of anticholinergic medications or use of sustained released medication on the accuracy of the 4-hour acetaminophen concentration.
- **Treatment:**
  - Failure to decontaminate patients who are less than 2 hours post ingestion.
  - Ending treatment for patients who have elevated transaminases or detectable serum acetaminophen concentrations.


Paracetamol Poisoning
Ask: - Amount ingested (A total dose of 6-7gm in adults is toxic &>150mg/kg in children)
- Time since ingestion
- Risk factors that increase risk of hepatotoxicity (patients on anticonvulsants or isoniazid, alcoholic, fasting, malnourished, hepatic and renal impairment)
Observe:- Nausea, vomiting, anorexia, malaise within 24 hrs
- Right upper quadrant pain and elevation in liver enzymes after 24 hrs
- Manifestations of severe hepatic disease after 72hrs
0- 4 hrs
4 -8 hrs
> 8 hrs
Pregnancy
- Do not induce vomiting
- GIT decontamination if < 1 hr
- Give activated charcoal (Single dose)
- Request serum paracetamol level & LFTs
- Give a loading dose of N- Acetyl cysteine 150 mg/kg IV
- Request >4 hrs peak plasma paracetamol level & determine toxicity risk from the Nomogram
- Request AST, ALT, Bilirubin,CBC,Platelets, PT, INR, Creatinine, Urea, RBS, Electrolytes
- Plasma paracetamol levels≅ or > 100 mg/L at 4 hrs and 15 mg/L at 15 hrs after ingestion (regardless of whether the patient is high risk or not) or intersection point of postingestion time vs. level above treatment line of the nomogram
- And/or Abnormal AST & ALT
- Plasma paracetamol levels<100µg/ml at 4hrs or intersection point of postingestion time vs. level below treatment line
- Normal LFT & other investigations
- Asymptomatic
Give N- Acetyl cysteine (NAC)
Do Not give N- Acetyl cysteine (NAC) and discharge the patient
Note: - In chronic overdose (>150-200mg/kg or 6-7g, ingested over 24 hrs) request serum Paracetamol & LFT and give NAC according to serum paracetmol level and liver enzymes.
- If extended release preparation, request 2hrly levels done for 8hrs and decide for NAC accordingly

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SALICYLATES

INTRODUCTION:

- Salicylates are widely used agents found in hundreds of over-the-counter (OTC) medications and in several prescription drugs, making poisoning with salicylates an important cause of morbidity and mortality.
- Salicylates are used as analgesic agents for the treatment of mild to moderate pain and as an anti-inflammatory agent. Salicylate toxicity is a complex problem that may occur after acute or chronic ingestion of salicylates.

TOXIC DOSE:

- The maximum adult dose should not exceed 3900 mg/24 hrs) for more than 10 days. Mild to moderate toxicity (150-300 mg/kg), severe (301-500 mg/kg) and fatal >500 mg/kg.

EPIDEMIOLOGY:

- Salicylates poisoning is common.
- Salicylates toxic manifestations following exposure are typically mild to moderate degree.
- Death develops in cases who are inadequately treated or in whom the clinical diagnosis is missed (usually the elderly with an underlying medical pathological condition and chronic salicylate toxicity).

CAUSES

- Salicylates poisoning is usually caused by a suicidal attempt.
- Chronic salicylates ingestion from therapeutic error is also common.
- Child neglect should be considered if the patient is less than 1 year of age; intentional attempt in patients over 6 years of age.

RISK FACTORS:

- Children between 4 and 12 years of age who ingest aspirin during a hyperthermic condition may be at risk for Reye's syndrome.
- Elderly patients with underlying pathological conditions have a 25-30% mortality rate from chronic salicylate intoxications.

DRUG AND DISEASE INTERACTION:

- Acetazolamide accelerate salicylate poisoning by enhancing CNS penetration.

MECHANISM OF TOXICITY:

- Salicylates inhibit cyclooxygenase enzyme, which results in a decrease in prostaglandin formation, and platelet dysfunction.
- Salicylates stimulate the respiratory center, leading to hyperventilation and respiratory alkalosis.
- They are weak acids and impair renal function, which leads to accumulation of inorganic acids.
- Salicylates also interfere with the Krebs cycle (limiting ATP production) and uncouple oxidative phosphorylation, resulting in lactic acidosis and the generation of heat.
- Finally, the induction of fatty acid metabolism yields ketone bodies. The outcome of these metabolic processes is a wide anion gap metabolic acidosis.
- Salicylate poisoning produces discordance between plasma and cerebrospinal fluid (CSF) glucose concentrations. Despite normal plasma glucose, CSF glucose may be low.

CLINICAL MANIFESTATIONS:

- Phase 1: Characterized by hyperventilation resulting from direct respiratory center stimulation, leading to respiratory alkalosis and compensatory alkaluria. Potassium, sodium and bicarbonate are excreted in the urine. This phase may last as long as 12 hrs.
- Phase 2: Characterized by paradoxic aciduria in the presence of continued respiratory alkalosis occurs when a sufficient amount of potassium has been lost from the kidneys. This phase may begin within 6 hrs and may last 12-24 hrs.
- Phase 3: Characterized by dehydration, hypokalemia, and progressive metabolic acidosis. This phase may begin 4-6 hrs after ingestion in a young infant or 24 hrs or more after ingestion in an adolescent or adult.

•Nausea, vomiting, diaphoresis, tinnitus, vertigo, hyperventilation, tachycardia, and hyperactivity are the earliest signs and symptoms of salicylate toxicity.

- Mild to moderate toxicity: GI disturbances, tinnitus, tachypnea, and respiratory alkalosis.
- Severe toxicity: Metabolic acidosis, hyperpnea, diaphoresis, fever, altered mental status, seizures, coma, rhabdomyolysis, cerebral edema, pulmonary oedema up to death.
- Chronic overdoses present more slowly and may be less pronounced, especially in the elderly, and may consist mainly of neurologic manifestations such as confusion, delirium, agitation, and seizures. Coagulopathy, hepatic injury, and dysrhythmias are rare complications of severe overdose.
- Delayed toxicity: The onset of clinical toxicity and peak serum levels may be delayed in patients with ingestion of sustained release or enteric coated salicylate, or if pylorospasm or pharmacobezoar develop. Patients should be monitored until serial serum salicylate levels are declining and clinical symptoms have improved.

DIFFERENTIAL DIAGNOSIS:

- Differential diagnoses include conditions that cause anion gap metabolic acidosis (e.g. iron, methanol, isopropanol, sepsis, and alcoholic ketoacidosis). Salicylate toxicity should also be considered in elderly patients with an altered mental status.

INVESTIGATIONS:

- **Routine**:
  - Monitor serum glucose.
  - Serum electrolytes, ALT, AST, PT, bilirubin, albumin, BUN, creatinine.
  - ABGs for patients with moderate to severe toxicity, and all patients undergoing urinary alkalinization.
  - EKG.
  - CBC, INR and PTT in patients with clinical evidence of moderate to severe toxicity.
  - Acetaminophen level.
  - Pregnancy test in all women of childbearing age.
  - 12-lead EKG.
  - Imaging studies: Chest X-ray, abdominal ultrasonography, endoscopy and obtain a CT brain for altered mental status.

- **Specific:**
  - Serial salicylate levels every 1-2 hrs until levels have peaked and are declining. Interpret the salicylate level in account of blood pH. A decreasing serum salicylate concentration can reflect either an increased tissue distribution with increased toxicity or an increased clearance with decreased toxicity. A decreasing serum salicylate level accompanied by a decreasing or low blood pH should be presumed to reflect serious or worsening situation, not an improvement. Blood salicylate concentration 15-25 mg/dl is considered within therapeutic range. Concentrations >25 mg/dl are associated with signs and symptoms of toxicity.

Admission criteria:

- Admit patients with major signs and symptoms (e.g., neurologic, cardiopulmonary, and metabolic) to an intensive care unit under the care of a medical toxicologist.
- Admit patients with minor signs and symptoms (e.g., tinnitus, nausea) to an observational unit or medical ward.
- Admit the following patients, regardless of salicylate levels:
  1. Infants and elderly individuals.
  2. Individuals with chronic salicylism.
  3. Ingestion of sustained-release products.

TREATMENT:

Stabilization:

- ABCs: Airway, breathing, and circulation should be evaluated and stabilized as necessary.
  - Patients who are comatose or presenting with altered mental status may need mechanical respiratory support and endotracheal intubation. If the patient requires intubation, monitor end-tidal CO2 and arterial blood gases frequently and maintain the preintubation minute ventilation to prevent severe acidosis.
  - Dehydration, concomitant electrolyte abnormalities, and hypoglycemia must be immediately corrected.

Decontamination:

- Activated charcoal (AC) adsorbs salicylates effectively and should be given (1 gm/kg up to 50 gm PO) within 1-2 hrs of ingestion to patients who can protect their airway and are not actively vomiting

and all intubated patients via orogastric tube. Patients who present after 2 hrs may benefit from AC because of delayed absorption due to enteric-coated tablets, pylorospasm, or bezoar formation.

- Multiple doses of AC if no contraindication: 25 gm by mouth q 2 hrs for 3 doses or 50 gm/PO q 4 hrs for 2 doses after the initial dose is given.
- Whole bowel irrigation (WBI) is not routinely used for salicylate toxicity but can be considered for massive ingestions of sustained preparation or enteric-coated drugs in an alert and cooperative patient.

Symptomatic:

- Monitor with CVP especially in patients with cardiac disease, non cardiogenic pulmonary oedema, and renal compromise.
- Correct dehydration with 0.9% saline 10 to 20 mL/kg/hr over 1-2 hrs until a good urine flow is obtained (at least 3 to 6 mL/kg/hr).
- Correct acidosis by administering 1-2 mEq/kg $NaHCO_3$ by IV bolus and begin urinary alkalinization.

Specific:

Alkalinization by sodium bicarbonate

Indications:

1. Serum salicylate >30 mg/dL and rising.
2. CNS symptoms and signs and tachypnea regardless of salicylate level.

Aim: To treat and prevent acidemia and to promote salicylate elimination by the kidneys.

Goal: to keep urine PH 7.5 - 8. Arterial PH should not rise above 7.55.

Contraindications: Renal failure, heart failure, and NCPE.

Method: Place 150 mEq (3 ampoules of 8.4%) of $NaHCO_3$ in 1 liter of D5W to provide an isotonic solution and 20-40 mEq of potassium chloride/ liter are added as needed to maintain normokalemia. Administer 10 to 20 mL/kg initially as a bolus, and then infuse at 2-3 mL/kg/hour. The rate of infusion should be sufficient to induce a urine output of 2-3 mL/kg/hr. Urine pH should be checked frequently every 1-2 hrs.

N.B. Monitor closely fluid overload, hypokalemia, hypocalcaemia and hypernatremia.

N.B. Hypokalemia and dehydration limit the effectiveness of urine alkalization.

Hemodialysis

Indications:

1. Patients with high serum salicylate levels (greater than 90 to 100 mg/dL after acute overdose, or 50 - 60 mg/dL with chronic intoxication).
2. Significant CNS abnormalities such as altered mental status, cerebral edema, or seizures.
3. Acute lung injury or respiratory failure.
4. Impaired glomerular filtration rate not responding to volume repletion.
5. Deteriorating clinical condition.
6. Significant hyperthermia (an indicator of mitochondrial toxicity from salicylates)
7. Co-ingestion of a substance that may exacerbate salicylate toxicity.
8. Refractory/profound acidemia.
9. Refractory/profound electrolyte disturbance.
10. Inability to administer sodium bicarbonate as in cases of renal insufficiency/failure or pulmonary edema.
11. Rising serum salicylate concentrations inspite of sodium bicarbonate administration

- Follow Up

- **Patient Monitoring:**
  - Continuous respiratory and cardiac monitoring should be done in symptomatic cases.
  - Patients should be revaluated frequently for abnormal mental status development and should have serial detection of serum electrolyte and salicylate levels.
  - Patients with rising salicylate levels, disturbed consciousness level, seizure, acute respiratory distress syndrome, or respiratory acidosis should be close monitored in an intensive care unit.
- **Expected Course and Prognosis:**
  - Acute salicylates intoxication typically starts within hours of salicylates ingestion and resolves within 24-48 hours depending on severity of salicylates toxicity; a complete recovery is usually expected.

- Chronic salicylates intoxication may start within days to weeks of salicylate ingestion and recovers over 48-72 hours once treatment is started.
- Permanent complications of hypoxia or cerebral edema may present.

- **Discharge Criteria/Instructions**
  - From the emergency department.
    Asymptomatic or minimally symptomatic cases may be discharged after gastrointestinal decontamination procedure, close observation for 4-6 hours, and a psychiatric assessment, provided that serial salicylate levels decreased significantly and acid-base status condition is normal.
  - From the hospital.
    Asymptomatic cases may be discharged after signs of poisoning resolve, serum electrolytes and renal function return to normal baseline, serial serum salicylate levels decreased to 30 mg/dl, and a psychiatric assessment is completed, if required.

COMMON PITFALLS:

- The nomogram is not useful; it can both overestimate and underestimate the severity of toxicity.
- Single determinations of salicylate levels are not sufficient because absorption may be delayed and erratic.
- Do not discharge patients unless it is clear that serial salicylate concentrations are declining.
- Sedation or intubation of the patient could lead to compromises in the patient's own respiratory drive, and has been associated with abrupt decompensation likely due to worsening metabolic acidosis and increasing the salicylate concentration in the CNS. If the patient requires intubation, it is imperative that respiratory alkalosis be maintained.
- Hypokalemia will interfere with urinary alkalinization.
- In young children, the initial respiratory alkalosis is transient. They often have a predominant metabolic acidosis (and in severe cases also respiratory alkalosis) on presentation.

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NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

INTRODUCTION:

- Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most common classes of medications prescribed. Despite the high rates of acute ingestion, few patients experience poor outcomes, and most require no medical intervention or supportive care alone.

TOXIC DOSE:

- In general ingestions of less than 100 mg/kg of most NSAIDs (except mefenamic acid and phenylbutazone) are unlikely to cause any significant toxicity. Massive overdoses that produce severe clinical toxicity are seen with ingestions greater than approximately 400 mg/kg.

EPIDEMIOLOGY:

- Non-steroidal anti-inflammatory drugs poisoning is common.
- Toxic manifestations following exposure are typically mild, with death occurring in rare conditions secondary to gastrointestinal bleeding effect.

CAUSES:

- Pattern of poisoning is usually accidental in pediatrics, intentional in adults.
- Child neglect or abuse should be considered if the patient is less than 1 year of age.

DRUG AND DISEASE INTERACTIONS:

- Alcoholics and cases with peptic ulcer are predisposed to gastrointestinal bleeding.
- Advanced age or preexisting renal impairment predispose to renal intoxications.
- Use with anticoagulants elevates the risk of bleeding tendency.

MECHANISM OF TOXICITY:

- Many of the adverse effects, and probably all or most of the acute toxicities of the NSAIDs, are associated primarily with the inhibition of cyclooxygenase 1 (COX-1). However, the high anion gap metabolic acidosis that rarely occurs with NSAIDs overdose results from the formation of weakly acidic NSAID metabolites, hypotension, and relative hypoxia. There is no sufficient evidence to point that inhibition of COX-1 itself is responsible for the production of the metabolic acidosis.

CLINICAL MANIFESTATIONS:

- The most common signs and symptoms are generally nonspecific and include nausea, vomiting, drowsiness, blurred vision, and dizziness.
- Less than 0.5% of these patients experience severe harm (e.g., hypothermia, convulsions, metabolic acidosis, coma and acute renal failure). Mefenamic acid ingestion commonly presents with convulsions.
- CVS: Hypotension and cardiovascular collapse have been reported following massive ibuprofen overdose.
- CNS: ataxia, nystagmus, headaches, and disorientation, convulsions and coma.
- Hematological: Aplastic anemia, bleeding gums, diffuse petechial rash and agranulocytosis after ingestion of phenylbutazone.
- Allergic reactions: Urticaria, asthma and anaphylaxis.
- Acid base abnormalities: An increased anion gap metabolic acidosis may be seen after large ingestions of NSAIDs, particularly ibuprofen, naproxen, and phenylbutazone.
- EKG and electrolytes: Cardiac dysrhythmias and electrolyte abnormalities.
- Evidence of impaired renal function (increased serum creatinine, hyperkalemia, decreased urine volume, or weight gain).

INVESTIGATIONS:

- **Routine:**
  - Blood glucose, to rule out hypoglycemia as the cause of any alteration in mental status.
  - Acetaminophen and salicylate levels, to rule out these common co-ingestions
  - EKG, to rule out conduction system poisoning by coingestants that affect the QRS or the QTc intervals.
  - Pregnancy test in all women of childbearing age
  - In symptomatic patients and those with large ingestions:
    1. Tests of renal function (BUN, creatinine), Serum electrolytes and arterial blood gases (ABGs) should be obtained.
    2. In bleeding patients, hemoglobin and platelet counts should be measured.
- **Specific:**
  - NSAID serum concentrations are generally not helpful.

TREATMENT:

- **Stabilization:**

  ABCs: Airway, breathing, and circulation should be evaluated and stabilized as necessary.

- **Decontamination:**

  Activated charcoal (AC) in patients who present within 2 hrs of an acute ingestion, unless specific contraindications exist e.g., bowel obstruction, perforation, aspiration risk, etc.

- **Supportive treatment:**

  1. Correction of metabolic acidosis by NaHCO3.
  2. Seizures are treated in standard fashion with benzodiazepines.
  3. Hypothermia generally responds to active external warming (e.g., heating blanket).
  4. Hemodialysis in patients with acute renal failure.

- Observation 4-6 hrs for patients with minor ingestions who are asymptomatic.
- A 24-hour observation is recommended in cases of mefenamic acid and phenylbutazone. Patients who present with signs of severe toxicity (e.g., pH <7.3, acute renal dysfunction, altered mental status), suicidal patients, and with other medical or psychosocial concerns should be admitted.

- FOLLOW UP:

- **Patient monitoring**
  - Respiratory function tests, CNS depressed condition, and acid-base status should be monitored in symptomatic cases.
- **Expected course and prognosis**
  - Peak effects usually develop within hours.
  - Most patients recover within 24 hours with supportive care.
  - Possible complications are gastrointestinal bleeding and renal impairment.
- **Discharge Criteria and instruction**
  - From the emergency department. Asymptomatic cases without documented metabolic acidosis may be discharged after decontamination procedure, observation for four hours, and psychiatric assessment, as indicate.
  - From hospital. Patients may be discharged when mental condition has returned to normal status, renal function has stabilized, and gastrointestinal bleeding has completely resolved.

PITFALLS:

- **Diagnosis**
  - Because cases usually misidentify analgesics, the physician needs to rule out acetaminophen and salicylate as co-ingestants possibilities.
- **Follow-Up**
  - Because delayed renal and hepatic toxic manifestations may develop after overdose ingestion of phenylbutazone, patients should be close followed for several days.

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FOODS AND DIETARY AGENTS

VITAMINS

INTRODUCTION:

Description:

- Acute toxicity is uncommonly after ingestion of vitamin products that do not contain iron. Vitamins A and D may produce toxicity, but usually only after chronic use. Serious poisoning has been reported in individuals attempting to mask urine drug screens by ingesting large quantities of niacin to adulterate urine sample.

Forms and uses:

- Although there are hundreds of formulations, the primary vitamins involved here are vitamin A, C, D, E, folic acid, thiamine (B1), riboflavin (B2), cyanocoblamin (B12), biotin, niacin, pantothenic acid, and pyridoxine (B6).

Toxic dose:

- A single ingestion must be very large to cause toxicity.
- A chronic ingestion of large amount may develop poisoning.
- **Vitamin A.**
  - Acute ingestion of more than 12,000 IU/kg is considered toxic.
  - Chronic ingestion of more than 25,000 IU/d for 2-3 weeks may develop toxicity.
- **Vitamin C.**
  - Acute intravenous doses of more than 1.5 g and chronic ingestion of more than 4 g/day have develop nephropathy.
- **Vitamin D.**
  - Acute ingestion is highly unlikely to develop toxicity.
  - In pediatrics, chronic ingestion of more than 5000 IU/d for several weeks may develop in toxicity (adults >25,000 IU/d).
- **Niacin.**
  - Acute ingestion of more than 100 mg may produce a dermal flushing reaction. Immediate-release products are more likely to develop flushing than are the timed-release preparations.
  - Ingestion of 2.5 g develops nausea, vomiting, dizziness, hypoglycemia followed by hyperglycemia, and coagulopathy.

- **Pyridoxine**.
  - Chronic ingestion of 2-5 g/d for several months has developed in neuropathy.

Pathophysiology:

- **Vitamin A.**
  - The mechanism by which excessive amounts of vitamin A develop increased intracranial tension is unknown.
- **Vitamin C.**
  - Chronic excessive use and large IV doses can develop increased levels of the metabolite oxalic acid. Urinary acidification stimulates calcium oxalate crystal formation, which can lead to nephropathy or acute renal impairment.
- **Vitamin D.**
  - Chronic ingestion of excessive amounts of vitamin D accelerates calcium absorption and produces hypercalcemia.
- **Niacin**.
  - The most common side effects of niacin are cutaneous flushing and pruritus mediated by prostaglandin release.
- **Pyridoxine.**
  - Chronic overdose may alter neuronal conduction velocity, resulting in paresthesias and muscular incoordination.

Epidemiology:

- Toxicity is common in Saudi Arabia and toxic effects are very rare.

Causes:

- In children, acute toxicity is usually an unintentional over dose

CLINICAL MANIFESTAIONS

- Most acute overdoses of multivitamins are associated with nausea, vomiting, and diarrhea.
- **Vitamin A.**
  - Chronic vitamin A poisoning is characterized by dry, peeling skin; alopecia; and signs of increased intracranial tension (headache, disturbed consciousness level, and blurred vision [pseudotumor cerebri]). Bulging fontanelles have been described in infants. Hepatic impairment may develop jaundice and ascites.

- **Vitamin C.**
  - Calcium oxalate crystals may develop acute renal impairment or chronic nephropathy.
- **Vitamin D.**
  - Chronic excessive use of vitamin D is accompanied with hypercalcemia, producing weakness, disturbed mental condition, GI upset, renal tubular impairment, and occult cardiac dysrhythmias.
- **Vitamin E.**
  - Chronic excessive use of vitamin E can develop nausea, headaches, and weakness.
- **Vitamin K.**
  - Vitamin K can develop hemolysis in newborns (especially if they are G6PD deficient).
- **Niacin**
  - Acute ingestion of niacin, but not niacinamide (nicotinamide), may develop unpleasant, dramatic cutaneous flushing and pruritus that may persist for a few hours.
  - Intentional ingestion of large amounts in an attempt to produce a negative urine drug screen "adulteration" has caused nausea, vomiting, abdominal pain, palpitations, dizziness, and hypoglycemia, followed by persistent hyperglycemia, anion gap metabolic acidosis, hypotension, and coagulopathy.
  - Chronic excessive use (particularly of the sustained-release form) has been associated with hepatitis.
- **Pyridoxine.**
  - Chronic excessive pyridoxine use may produce peripheral neuropathy.
- **Vitamins.**
  - Large doses of B vitamins may deepen the yellow color of urine, and riboflavin may develop yellow perspiration.

INVESTIGATIONS

General Tests:

- Useful laboratory tests in such cases involve CBC, electrolytes, glucose, BUN, calcium, creatinine, liver aminotransferases, and urinalysis.

Specific Tests:

- **Vitamin A.**
  - Serum vitamin A (retinol) or carotenoid assays may help in the diagnosis of hypervitaminosis A.
- **Vitamin D.**
  - Levels of 25-hydroxy vitamin D are helpful in assessing excessive intake and are increasingly available through clinical laboratories

TREATMENT

A. Emergency and supportive measures.

- **Fluid loss.** Treat fluid losses caused by gastroenteritis with replacement therapy of IV crystalloid solutions.
- **Increases intracranial tension.** Treat vitamin A-induced elevated intracranial tension if they develop.
- **Hypercalcaemia.** Treat vitamin D-induced hypercalcemia if they develop.
- **Pruritus**. Non-steroidal anti-inflammatory agents may prevent or alleviate prostaglandin-mediated niacin flushing or pruritus.

B. Specific drugs and antidotes.

- There is no specific antidote for hypervitaminosis toxic conditions.

C. Decontamination procedures.

- Usually, gut decontamination is unnecessary unless a toxic dose of vitamin A or D has been reported or the product contains a toxic amount of iron.

D. Enhanced elimination procedures.

- All form of elimination enhancement such as, forced diuresis, dialysis, and hemoperfusion are of no clinical benefit.

FOLLOW UP

Expected course and prognosis

- Most cases can be expected to make a full recovery with cessation of vitamin supplement and with supportive care.

Discharge criteria/instructions.

- Asymptomatic cases may be discharged after from emergency department or hospital following evaluation of coingestants and psychiatric evaluations, if required.

Patient education.

- The case should be instructed to discontinue taking the vitamin formulation involved.

PITFALLS

- Vitamin and “alternative” medications are not considered a medicine by the patient. The history should be actively specify this information.

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IRON

INTRODUCTION:

- Iron is found in several different forms and in different medicinal formulations. Iron poisoning is particularly common among children. It is valuable to identify the amount of elemental iron not the iron salt.
- The most common iron formulations used are ferrous sulfate, ferrous gluconate and ferrous fumarate which contain 20%, 12% and 33% elemental iron respectively.
- To children, iron tablets may resemble candy. Multivitamins used by mothers during pregnancy are the main source of lethal ingestions among children. Children's chewable multivitamins usually have small amounts of iron therefore toxicity rarely occurs.
- Sustained release formulations or enteric-coated iron preparations may be absorbed at a slower rate. This is an important consideration when interpreting serum iron concentrations.

Toxic dose:

- 20 to 60 mg/kg is mildly to moderately toxic and > 60 mg/kg can cause severe symptoms and mortality.

EPIDEMIOLOGY

- Iron poisoning is common.
- Toxic manifestations following exposure are typically mild to moderate degree.
- Death develops as a result of large amount of iron ingestions with delayed patient presentation.

CAUSES

- Acute iron overdose is usually suicidal in adults and accidental in children.
- The possibility of child neglect should be considered in patients under 1 year of age; suicide attempt in patients over 6 years of age.

MECHANISM OF TOXICITY:

- Iron produces a direct corrosive effect on mucosal tissue and may result in hemorrhagic necrosis and perforation. Hypovolemia can occur as a result of fluid loss from the gastrointestinal tract.
- Iron absorbed in excess of protein binding capacity causes cellular dysfunction, resulting in lactic acidosis and necrosis. Iron can induce oxidative stress and free-radical production.

CLINICAL MANFESTATIONS:

Clinical course

- Gastrointestinal (GI) phase: (0.5 to 2 hrs) includes vomiting, abdominal pain hematemesis, diarrhea (can be bloody or dark coloured), lethargy, shock, acidosis, and coagulopathy. Iron can cause necrosis to the GI tract as a result of it`s corrosive effect on the GI mucosa. Loss of large amounts of fluids or blood could lead to shock. Severe gastrointestinal hemorrhagic necrosis could result from acute iron toxicity.
- Latent phase: (6-24 hrs) includes apparent recovery. Continue to observe patient closely.
- Shock and metabolic acidosis phase: (6-72 hrs) includes severe shock, metabolic acidosis, cyanosis, and fever. Increased total peripheral resistance, decreased plasma volume, hemoconcentration, decrease in total blood volume, hypotension and CNS depression have been reported.
- Hepatotoxicity/hepatic necrosis phase: (2-4 days) includes possible hepatotoxicity. Thought to be a direct action of iron on the mitochondria. Acute lung injury may also occur at this stage.
- Bowel obstruction phase: (days to weeks) includes GI scarring and strictures. GI obstruction as a result of gastric or pyloric scarring may occur as a late complication of iron`s corrosive effect. This can also be seen in sustained release preparations.

INVESTIGATIONS:

- Recommeneded for ingestions of more than 40 mg/kg of elemental iron.

Routine:

- Serum electrolytes, BUN, glucose, ALT, AST and bilirubin.
- ABG in moderately and severely poisoned patients (anion gap metabolic acidosis).
- CBC, PT and PTT.
- Urine analysis: With the use of deferoxamine, it binds free iron creating ferrioxamine which is excreted in the urine. Urine containing ferrioxamine may be brick orange or "vin rosé"in colour.

Specific:

- Measurement of serum iron concentration (SIC) is useful for confirming the diagnosis of iron ingestion. The best estimate of the severity of the overdose can be determined by performing a SIC measurement within 4-6 hrs of the ingestion. For slow-release iron, a SIC should be obtained at 8 hrs. It cannot always be correlated with the severity or the clinical phase of iron intoxication.

Radiographic evaluation:

- Plain abdominal X-ray for patients who may have ingested more than 40 mg/kg of elemental iron or who have significant symptoms should be performed. The presence of radiopaque pills in the stomach confirms the ingestion of iron. However, many liquid iron preparations and chewable vitamins with low concentrations of iron are not visible, it does not necessarily mean that the ingestion was insignificant.

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis of iron poisoning is broad given the range of clinical findings (high anion gap metabolic acidosis, hepatotoxic poisons, GIT irritants).

TREATMENT

Stabilization:

- Assess airway, breathing, and circulation; stabilize as necessary

Decontamination:

- The decontamination modality of choice is whole bowel irrigation (WBI) using a naso-gastric colonic lavage solution 30mL/kg/hr until rectal effluent is clear (contraindicated if there are signs of bowel obstruction or hemorrhage).
- Charcoal is of NO benefit.
- WBI is indicated:
  - If X-ray reveals tablets, or capsules ingested
  - In symptomatic patients

Antidote:

Desferrioxamine

- It is an iron-chelating agent that when binds to iron forms a non harmful water soluble desferroxamine-iron complex, that is easily excreted by the kidney.

Administer desferrioxamine if:

- Serum iron levels > 90 μmol/L
- Serum iron level 60 - 90 μmol/L and tablets are visible on X-ray or patient is presenting with nausea, vomiting, diarrhea, abdominal pain, haematemesis and fever.
- Patients presenting with serious or worsening symptoms of altered conscious state, hypotension, tachycardia, tachypnoea and metabolic acidosis pH< 7.1.

Dose:

- Desferrioxamine 15 mg/kg/hr IV. Reduce the rate after 4-6 hrs so that the total intravenous dose does not exceed 80 mg/kg/24 hrs.

- If oliguria or anuria develops, peritoneal dialysis or haemodialysis are warranted to remove ferrioxamine (The compound formed after chelation of iron).
- Determination of the endpoint for chelation therapy is difficult. Significant poisoning usually requires 12 - 16 hrs. However, it is recommended to continue desferrioxamine until:
  - Patient is asymptomatic.
  - Anion-gap metabolic acidosis is resolved.
  - Iron level is < 54 μmol/L.
- As desferoxamine has been associated with pulmonary toxicity with the prolonged use more than 24 hrs, consult with the medical toxicologist when indicated.

Pregnancy:

- Use of desferoxamine for iron poisoning with pregnancy improves maternal condition therapy improves condition for the fetus.

Supportive care:

- Volume resuscitation to maintain euvolemia. Hypovolemic shock is the major cause of mortality during the first phase of iron intoxication. Patients who present with severe gastrointestinal symptoms require urgent intensive management to maintain effective circulating blood volume.

FOLLOW UP:

PATIENT MONITORING

- Iron level, CBC, serum electrolytes, and hemodynamic close monitoring should be repeated frequently over the first few hours in patients with acute iron toxic effects to assess response to therapeutic maneuver.
- If abdominal radiographs appear tablets, repeat radiographic films are indicated to assess the efficiency of decontamination.

EXPECTED COURSE AND PROGNOSIS

- Most patients develop gastrointestinal manifestations, are treated with deferoxamine therapy, and resolve over 12-48 hours.
- In severe cases, manifestations develop rapidly and may lead to a course persisting several days and complicated by multiple complicating effects of shock.
- In iron poisoning patients without shock or coma, mortality is < 1%.
- Shock or coma predicts mortality of 50% with supportive treatment, 10% with supportive treatment and deferoxamine therapy.
- Scarring from local corrosive iron effects may lead in gastrointestinal obstruction 4 to 6 weeks after severe iron toxicity.

DISCHARGE CRITERIA/INSTRUCTIONS

Patients may be discharged after observing for at least 6 hours post ingestion, if they have all of the following:

-Absence of vomiting
-Amount of ingestion is < 20 mg/kg of elemental iron
-Serum iron level < 300 mcg/dL at 4-6 hours post ingestion.

Suicidal patients should be evaluated by a psychiatrist

COMMON PITFALLS

- Failure to provide adequate amounts of intravenous fluids.
- Delaying the administration of desferrioxamine till the serum iron level is obtained in patients that are already symptomatic.
- Making treatment decisions based on the total iron binding capacity.
- Failure to recognize patients in the latent phase
- Excessive reliance on the SIC in management decisions
- Inaccurate calculation of the dose of elemental iron ingested
- Inadequate desferrioxamine dose
- Giving prochlorperazine drug and desferrioxamine together
- Failure to appreciate that desferrioxamine may falsely lower serum iron concentration

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FOOD POISONING

INTRODUCTION:

- Food poisoning occurs as a result of ingesting food or water that contains bacteria, viruses, parasites or the toxins created by these germs. Most food poisonings are caused by common bacteria such as, staphylococcus or E coli.
- Food poisoning can affect one person or a group of people who share the same food. It is more commonly encountered after eating at picnics, school cafeterias, large social events and at restaurants.
- A food poisoning outbreak is defined by the following 2 criteria:
  - Similar illness, often gastrointestinal, in a minimum of 2 people.
  - Evidence of food as the source.

EPIDEMIOLOGY

- The true incidence of food poisoning is unknown because several cases are mild and unreported or misdiagnosed.
- Multiple cases presenting at the same time in roughly the same place typically result from a common exposure source.

CAUSES

- Food poisoning develops from ingestion of contaminated vegetables, fruit, salads, fried rice, pastries, corn flour, milk, cheese, and salads, or contaminated water.

DRUG AND DISEASE INTERACTIONS

- Toxic manifestations, especially dehydration, are more marked in pediatric and the elderly, although death from shock and fluid depletion is rare even in these populations.

MECHANISM OF TOXICITY:

- The pathogenesis of diarrhea in food poisoning could be classified into either non-inflammatory or inflammatory types.
- Non-inflammatory diarrhea is caused by the action of enterotoxins on the secretory mechanisms of the mucosa of the small intestine, without invasion. This results in large volumes of watery stools in the absence of blood, pus, or severe abdominal pain. Occasionally, profound dehydration may result. Examples include Vibrio cholerae, Enterotoxic Escherichia Coli, Staphylococcus, Giardia Lamblia, Cryptosporidium, Rotavirus, Norovirus, and Adenovirus.
- Inflammatory diarrhea is caused by the invasion and destruction of the mucosa by a cytotoxin. The colon or the distal small bowel are commonly involved. The diarrhea is often bloody mucoid with abundant leukocytes. Patients are commonly febrile and may exhibit a toxic appearance. Dehydration is less likely to be seen with the inflammatory than with noninflammatory diarrhea. Examples include

Campylobacter Jejuni, Vibrio Parahaemolyticus, Enterohemorrhagic and Enteroinvasive E Coli, Yersinia Enterocolitis, Entamoeba Histolytica, Salmonella and Shigella species.

CLINICAL MANIFESTATIONS:

- The clinical presentation of food poisoning may vary in degree and combination of symptoms. These symptoms may present as follows:
  - Abdominal pain: Most severe in inflammatory diarrhea; the
  - Presence of painful abdominal muscle cramps suggests underlying electrolyte loss.
  - Vomiting: A major presenting symptom of Staph Aureus, B Cereus, or Norovirus.
  - Diarrhea: Does not usually last more than 2 weeks.
  - Headache.
- Fever: The presence of fever suggests that it is an invasive disease or that the infection originated outside the GI tract.
- Stool changes: Bloody or mucousy if invasion of intestinal or colonic mucosa; profuse rice-watery if cholera or a similar process.
- Reactive arthritis: Seen with Salmonella, Shigella, Campylobacter, and Yersinia infections.
- Bloating: May be caused by giardiasis.
- Dehydration: Signs of dehydration (thirst, dizziness, light-headedness).
- More serious cases of food poisoning can result in life-threatening neurologic, hepatic, and renal syndromes leading to permanent disability or death.

ADMISSION CRITERIA

- Patients with hypotension.
- Severe electrolyte abnormalities.
- Respiratory distress or any other complication.

COMPLICATIONS:

- Dehydration is the most common complication.
- Less common complications:
  - Arthritis.
  - Bleeding.
  - Damage to the nervous system.
  - Kidney problems.
  - Hemolytic uremic syndrome (E Coli).
  - Swelling or irritation in the pericardium.
  - Guillain-Barré syndrome (Campylobacter infection)

		LIKELY MICROBES	INCUBATION PERIOD	LIKELY FOOD SOURCES
MAJOR PRESENTING SYMPTOM	Vomiting	S. aureus	1 to 6 hr.	Prepared Food, E.G., Salads, Dairy And Meat
		B. cereus	1 to 6 hr.	Rice, Meat.
		Norwalk-like viruses	24 to 48 hr.	Shellfish, Prepared Foods, Salads, Sandwiches And Fruits.
	Watery Diarrhea	C. perfringens	8 to 16 hr.	Meat And Poultry.
		Enterotoxigenic E. coli	1 to 3 days	Fecally Contaminated Food Or Water.
		Enteric viruses	10 to 72 hr.	Fecally Contaminated Food Or Water.
		C. parvum	2 to 28 days	Vegetables, Fruit, Unpasteurized Milk And Water.
		C. cayetanensis	1 to 11 days	Imported Berries And Basil
	Inflammatory Diarrhea	Campylobacter spp	2 to 5 days	Poultry, Unpasteurized Milk, Water.
		Non-typhoidal salmonella	1 to 3 days	Eggs, Poultry, Meat, Unpasteurized Milk Or Juice And Fresh Produce.
		Shiga toxin-producing E. coli	1 to 8 days	Ground Beef, Unpasteurized Milk And Juice, Raw Vegetables And Water.
		Shigella spp	1 to 3 days	Fecal Contamination Of Food And Water
		V. parahemolyticus	2 to 48 hr.	Raw Shellfish

INVESTIGATIONS:

Routine:

- CBC with differential count.
- Serum glucose and Serum electrolyte assessment.
- BUN and creatinine levels.
- ALT, AST and Bilirubin.
- Obtain flat, upright abdominal radiographs if the patient experiences bloating, severe pain or obstructive symptoms or if the clinical picture suggests perforation and to document or rule out differential diagnosis.

Specific:

- Stool Gram staining for WBCs: To aid in the differentiation between invasive and noninvasive organisms.

- Microscopic examination of the stool: To help in the detection of any ova and parasites.
- Bacterial culture for enteric pathogens: Recommended when a stool sample shows positive results for WBCs or blood or if patients exhibit fever or symptoms persisting for longer than 3-4 days
- Blood culture in notably febrile patients.
- Clostridium difficile assay: To help exclude antibiotic-associated diarrhea in patients receiving antibiotics or in those with a history of recent antibiotic use.
- Ask for food samples and vomitus for analysis.

Others:

- You may check for levels of pseudo cholinesterase, carboxy hemoglobin (COHb), MetHb, iron, and lead. Whenever needed to document or rule out differential diagnosis.

TREATMENT:

Stabilization:

- Airway, breathing, and circulation (ABC) should be evaluated and stabilized as necessary.

Immediately rehydrate with:

- Oral rehydration mixtures to replace fluids and minerals lost through vomiting and diarrhea.
- If the patient has diarrhea and is unable to drink, you may need to administer intravenous fluids. Start IV infusion by 0.9% NaCl or ringers lactate, guided by the degree of dehydration, pH, urine output, and previous diseases (hypertension and CHF).
- Cases presenting with shock may be treated under central venous pressure (CVP) guide.

Supportive treatment:

- Antiemetic (metoclopramides), Antispasmodics, Antipyretics (paracetamol).
- Plenty of fluid and rest.
- Antibiotics may be started whenever possible as cephalosporin (for children) or quinolones (for adults) may be given for patients with fever, leucocytosis, and pus cells in stool (enteroinvasive FP). Do not give antibiotics for the toxigenic type of food poisoning.

PATIENT DISHCARGE:

- Discharge the patient when condition is stabilized, and no other differential diagnosis is still considered, blood pressure normalized, renal function and dehydration corrected, patient can depend on his oral hydration (no vomiting).

COMMON PITFALLS:

- Consider closer observation periods for the elderly, very young, chronically ill, immunosuppressed, or those who might be predisposed to dehydration.
- Inform patients that reheating food will not destroy the toxin.
- Contact your local public health department so that they may monitor for other possible outbreaks, especially if multiple patients are involved.

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BOTULISM

INTRODUCTION:

- Botulism is a potentially life-threatening neuroparalytic syndrome resulting from the effect of a neurotoxin released by the Clostridium botulinum bacteria.
- C. botulinum is a heterogeneous group of gram-positive, rod-shaped, spore-forming anaerobic bacteria.
- Several forms of botulism exist, including foodborne botulism, infant botulism, wound botulism, adult enteric infectious botulism, inhalational botulism (from bioterrorism events), and iatrogenic botulism (from cosmetic use of botulinum toxin).
- The spores of C. botulinum are heat resistant, and can survive heating at 100^{O}C at for five hours or more. On the other hand, spores can be destroyed by heating at 120^{O}C for five minutes.
- The C. Botulinum spores will germinate and grow into toxin-producing bacilli under the following conditions:
  1) Restricted oxygen exposure (either an anaerobic or semi-anaerobic environment)
  2) Low acidity (pH > 4.6) water
  3) A temperature of 25 to 37^{O}C for ideal growth; however, some strains may grow in temperatures as low as 4^{O}C.
- The toxin itself is tasteless and odorless. If ingested, the toxin is primarily absorbed by the stomach and small intestine, although the large intestine is capable of absorbing the toxin as well. The toxin is resistant to degradation by gastric acidity and human alimentary enzymes.

TOXIC DOSE:

- Botulinum toxin is perhaps the most potent poison known to man. A dose as low as 0.05 μg of toxin can be fatal.

EPIDEMIOLOGY:

- It is important to perform a thorough history to identify possible exposures in patients presenting with a syndrome suggestive of botulism. This includes a history of home canning, exposure to other possible food sources (including honey in infants <12 months of age), injection drug use, and cosmetic use of botulinum toxin.

MECHANISM OF TOXICITY:

- After entering the cell's cytoplasm, the toxin causes an irreversible modulation in stimulation-induced acetylcholine release in the same presynaptic nerve terminal.

CLINICAL MANIFESTATIONS:

Symptoms of botulism in adults

Time to symptom onset varies by route of exposure

Foodborne botulism

- Gastrointestinal symptoms often precede symptom onset
- Neurologic symptoms arise 12-36 hours after toxin ingestion (range 6 hours to 10 days)

Wound botulism

- Gastrointestinal symptoms absent
- Neurologic symptoms likely arise within 2 weeks of exposure (but incubation period not well defined)

Inhalational botulism

- Gastrointestinal symptoms absent
- Neurologic symptoms arise about 6 hours after exposure

Common symptoms

- Cranial nerve palsies are typically the first symptoms
- Blurry or double vision may indicate extraocular muscle paralysis
- Ptosis is a common early finding
- Facial weakness, difficulty speaking and difficulty swallowing may also occur
- Involvement of the autonomic nervous system may lead to dry mouth and throat (which can be mistaken for pharyngitis)
- Postural hypotension
- Nausea and vomiting
- Symmetric muscle weakness then progresses downward from the muscles of the head and neck to the feet
- Loss of head control may be notable early in course
- Weakness of the pharyngeal muscles may lead to airway collapse
- Weakness of chest wall muscles and diaphragm may also lead to respiratory distress or arrest
- Rate of descending paralysis varies from hours to days (likely dose related)
- Sensation and mental status are usually unaffected

Symptoms of botulism in infants

- In addition to neck and muscle weakness (floppy baby syndrome)

- Poor feeding
- Diminished suckling or ability to cry
- Constipation
- Respiratory distress

DIAGNOSIS:

A thorough history and physical examination are essential.

- A high degree of suspicion is needed for diagnosis as confirmatory testing takes > 1 day and immediate antitoxin treatment is needed
- Consider the diagnosis of botulism in patients presenting with a matching clinical syndrome
- Cranial nerve palsies, particularly when symmetric descending flaccid paralysis without sensory affection
- Potential epidemiological risk factor preceding gastrointestinal illness
- IV drug use, particularly heroin
- Age < 1 year, particularly if accompanied by honey ingestion
- Serum assays for botulinum toxin are often negative in cases of infant botulism. The diagnosis is confirmed by the isolation of C. botulinum spores from the stool and via the identification of botulinum toxin in stool samples. However, these tests take time.
- Thus, a presumptive diagnosis should be made based upon the clinical presentation and electrophysiologic findings (electromyogram [EMG]), while the confirmatory stool studies are pending.

DIFFERENTIAL DIAGNOSIS:

- Myasthenia gravis
- Lambert-Eaton myasthenic syndrome (LEMS)
- Tick paralysis
- Guillain-Barré syndrome, poliomyelitis, stroke, and heavy metal intoxication.
- Tetrodotoxin and shellfish poisoning and antimicrobial-associated paralysis.

TREATMENT:

Any patient presenting with clinical signs, symptoms, or history suspicious for botulism should be hospitalized immediately and closely observed for signs of respiratory failure.

Monitoring:

- Pulse oximetry, spirometry, arterial blood gas measurement, and clinical evaluation of ventilation, perfusion, and upper airway integrity.

- Respiratory failure the most common cause of mortality in these patients.
- Prompt intubation with mechanical ventilation will dramatically decrease the risk of mortality in patients with insufficient or worsening upper airway competency and those with a reduced vital capacity.
- Infants and severe cases may require prolonged mechanical ventilation.

Antitoxin:

- Equine serum heptavalent botulism antitoxin is used to treat children older than one year of age and adults; human-derived botulism immune globulin has been successfully used for infants less than one year of age.
- The antitoxin should be given to the patient as soon as possible and should not be delayed while awaiting results of diagnostic studies.
- For adults, one vial 10 ml should be administered intravenously (IV) diluted in 0.9% Saline and administered by slow IV infusion. A second vial may be administered within 2-4 hrs if symptoms worsen. For children aged 1-17 years, 20-100 percent of the adult dose should be given. For infants < 1 year of age, 10 percent of the adult dose should be given. There does not appear to be any benefit from additional doses.
- Antibiotics are not recommended for infant presenting with botulism or for adults with suspected gastrointestinal botulism as this could lead to lysis of intraluminal C. botulinum which could increase the amount of toxin available for absorption.

Other treatments:

- In cases of foodborne botulism, laxatives, enemas, or other cathartics may be given, provided no significant ileus is present.
- Patients presenting with wound botulism should have a thorough wound debridement, even if the wound appears unimpressive. These patients should receive tetanus boosters.

Prevention:

- The most significant aspect of botulism prevention is the proper handling of food and preparation. Good home canning techniques (e.g., following pressure canners' /cookers' instructions regarding minimum cooking time, pressure, and temperature) will destroy spores.
- Food from damaged cans should not be consumed. Botulism toxin is heat labile; therefore, boiling home-canned foods for at least 10 minutes before consumption will render the food safe.

- The prevention of infant botulism is limited to the avoidance of honey in infants less than 12 months.
- The most important measure for the prevention of wound botulism is prompt medical evaluation and treatment of infected wounds.

Recommendations:

- When botulism is suspected, the clinician should contact the Regional Health Authority immediately for assistance and to obtain a supply of antitoxin.
- If the clinical suspicion for botulism is high and symptoms are progressing, antitoxin should be administered as soon as possible and should not be delayed while awaiting results of diagnostic studies.

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PHARMACEUTICALS

ANTIDIABETIC DRUGS

(HYPOGLYCEMICS AGENTS)

INTRODUCTION:

- Sulfonylurea agents are commonly used in the treatment of type II diabetes mellitus. They can achieve euglycemia when used correctly. However, hypoglycemia may result if renal clearance is impaired or the patient does not eat as required. Sulfonylureas could often cause hypoglycemia with overdose or when ingested by nondiabetic patients.
- Biguanides which include phenformin and metformin are antihyperglycemic agents that are less likely to cause hypoglycemia. They are used as both monotherapy and in combination with other oral hypoglycemics. They can accentuate hypoglycemia induced by other types of antidiabetics. The most serious toxic manifestation from acute or chronic biguanide toxicity is lactic acidosis. Phenformin has been withdrawn from the market due to the high rate of lactic acidosis assocaited with the use of the drug. Currently, metformin is the principal biguanide in clinical use.

TOXIC DOSE:

- One pill may cause hypoglycemia in a non-diabetic child or adult.

PATHOPHYSIOLOGY:

- Sulfonylurea agents cause hypoglycemia by:

  ↑Stimulating pancreatic insulin release

  ↓Suppressing glucagon release.

EPIDEMIOLOGY:

- Oral hypoglycemic poisoning is common.
- Hypoglycemic toxic effects are typically mild following accidental exposure, but may be severe after large, intentional ingestion.
- Death from oral hypoglycemic medication is rare, occurring in untreated cases with severe hypoglycemia.
- Infants and children have smaller glycogen stores than adults and are prone to more developing hypoglycemic manifestations.

RISK FACTORS:

- Conditions that decrease sulfonylurea excretion (hepatic and renal impairment)

- Conditions deplete glycogen stores (starvation, alcohol abuse, hepatic disease) predispose to hypoglycemic manifestations.

DRUG AND DISEASE INTERACTION:

- Hypoglycemia may be accelerted by cimetidine, ethanol, insulin, salicylates, phenylbutazone, sulfonamides, beta-blockers, enalapril, chloramphenicol, gemfibrozil, ranitidine, clofibrate, and warfarin.
- A disulfiram-like response manifestation may occur upon intake of alcohol.

MECHANISM OF TOXICITY:

- Sulfonylureas reduce blood glucose levels mainly through stimulating endogenous pancreatic insulin secretion and secondarily through enhancing the sensitivity of peripheral insulin receptors and reducing glycogenolysis.
- Biguanides reduce hepatic glucose production, absorption of glucose from the intestine, while promoting peripheral glucose uptake and utilization. It does not stimulate insulin release. Therefore, it is not likely to produce acute hypoglycemia. Severe lactic acidosis is a rare but very serious side effect of metformin overdose.
- Metformin Associated Lactic Acidosis (MALA):
    - Metformin promotes the conversion of glucose to lactate in the splanchnic bed of the small intestine. Metformin also inhibits mitochondrial respiratory chain complex, leading to decreased hepatic gluconeogenesis from lactate, pyruvate, and alanine.
    - Clinically significant accumulation of lactate usually occurs with the presence of other comorbid medical conditions, such as, renal insufficiency, liver disease, alcohol abuse and heart failure.
    - Acarbose is an α -glucosidase inhibitor reduces postprandial blood glucose concentrations through delaying the digestion of ingested carbohydrates,
    - Troglitazone reduces hepatic glucose output and improves the response to insulin at the cellular level.

CLINICAL MANIFESTATIONS:

- Vital Signs: Hypothermia, tachypnea, hypertension, tachycardia
- Pupils: May be normal or fixed and dilated
- Cardiovascular Dysrhythmias: Atrial fibrillation, ventricular ectopy
- Skin: Decreased turgor, Diaphoresis, Pallor
- Neurologic: Tremor, agitation, dépressions, coma, siezures, neurologic déficits
- The onset of hypoglycemia may be delayed depending on the type of drug used and the route of administration. Manifestations of hypoglycemia include agitation, confusion, coma, seizures, tachycardia, and diaphoresis.
- The serum levels of potassium and magnesium may be decreaseed.
- Note that manifesations of hypoglycemia may be masked in patients receiving β -adrenergic blocking agents.
- Metformin or phenformin induced lactic acidosis may present with nonspecific symptoms such as malaise, vomiting, myalgias, and respiratory distress.

- Thiazolidinediones and α glucosidase
  - Overdose with thiazolidinediones and α glucosidase inhibitors does not usually result in acute toxicity, yet hepatic dysfunction may occur with chronic use.

DIFFERENTIAL DIAGNOSIS:

- Overdose involving sulfonylureas or insulin should be considered in any patient with hypoglycemia. Other causes of hypoglycemia that should be suspected include alcohol ingestion (especially in children) and fulminant hepatic failure.
- Diabetic patients presenting with an elevated anion gap metabolic acidosis may have MALA or diabetic ketoacidosis. The condition can be dissected based on the history (concurrent illness, recent oral intake, and intentional ingestion) and the presence or absence of hyperglycemia, ketosis and hyperlactatemia.

INVESTIGATIONS:

Routine:

- Liver function tests, BUN, creatinine and urine output to assess kidney perfusion.
- Random blood glucose.
- Serum electrolytes.
- Arterial blood gases or oximetry.
- EKG monitoring
- Pregnancy test for all women of childbearing age.
- If metformin is suspected, serum lactate level and arterial blood gases should be assessed.

Specific:

- The mainstay of laboratory investigations is frequent monitoring of serum blood glucose levels. Concentrations of many agents can be determined in laboratories, but have little utility in acute clinical management.

TREATMENT

Stabilization:

- Assess airway, breathing, and circulation; stabilize as necessary. Treat coma and seizures if they occur.

Decontamination:

- Oral activated charcoal is the mainstay of decontamination in case of ingestion of large or unknown amounts of oral hypoglycemic agents unless there are specific contraindications such as, bowel obstruction or GI perforation.
- The clinician must assess aspiration risk, including mental status and ability to protect the airway, in all patients before any attempts to administer AC.

Specific therapy:

- Administer glucose as soon as possible after drawing a baseline blood sample for later blood glucose determination. For adults, administer 50% dextrose (D50W), 1-2 mL/kg; for children, administer dextrose 25% (D25W), 2-4 mL/kg.
- Monitor serum glucose levels closely for several hours after the last infusion of dextrose. Administer repeated glucose boluses

and 5–10% dextrose (D5W–D10W) as needed to stabilize the serum glucose levels at or above 100 mg/dL.

Octreotide:

- Patients with a sulfonylurea overdose and symptomatic hypoglycemia should be treated with both intravenous dextrose and octreotide. Octreotide inhibits insulin release from pancreatic β -islet cells through acting as a somatostatin analogue. In adults, the dose of octreotide is 50-150 µg IM, or SC, injection q 6 hrs. In children the dose is 1 - 1.5 µg/kg (up to 150 µg) q 6 hrs. Octreotide may also be given as an IV bolus over several minutes or by continuous IV infusion.
- Octreotide should be administered for 24 hrs. After octreotide is discontinued, the patient is monitored for hypoglycemia for another 24 hrs to ensure there is no remaining drug or active metabolite. If hypoglycemia recurs during this period, we suggest restarting octreotide therapy for another 24 hrs. In addition, two serum glucose measurements should be obtained 30 minutes apart during the first hour, and every 4-6 hrs thereafter provided euglycemia is maintained
- Patients with a single episode of hypoglycemia during therapeutic sulfonylurea use (not overdose) are treated by intravenous dextrose to correct symptomatic hypoglycemia, no need for octreotide and follow-up blood glucose level.
- Use sodium bicarbonate only for patients with severe metformin-associated metabolic acidosis (arterial pH below 7.10), with the target of maintaining the pH above 7.15, until the acute toxicity resolves. Excessive admininstration of sodium bicarbonate may increase intracellular acidosis.

Hemodialysis for metformin:

- Hemodialysis has shown success in treating patients with metformin-associated lactic acidosis due to chronic use or acute overdose. Hemodialysis may be used in patients who are critically ill, who have a severe metabolic acidosis (pH < 7.1), who fail to improve with supportive care, or in whom renal insufficiency is present.

- Hemodialysis should be conducted with the use of bicarbonate buffer, as the main benefit of hemodialysis is in correcting the metabolic acidosis rather than in removing metformin.

N.B.

- A person who ingests sulfonlyureas should be admitted if:
  - Hypoglycemia develops.
  - It is a deliberate overdose.
  - The patient is a child, even in the absence of hypoglycemia.
  - The onset of lactic acidosis may take several hours. So patients presenting with an acute ingestion should be kept under observation for at least 6-8 hrs. Patients who have no clinical manifestations and have stable blood glucose and a normal acid-base status may be discharged after 6-8 hrs of stablity.

COMMON PITFALLS:

- Unawareness with the fact that severe hypoglycemia can lead to focal neurological deficits and focal seizures.
- Failure to observe patients with sulfonylurea or meglitinide overdose for at least 8 hrs.
- Administering prophylactic dextrose to patients with sulfonylurea or meglitinide overdose who are asymptomatic or euglycemic.
- Failure to appreciate that excessive glucose administration stimulates insulin secretion and can result in hypoglycemia especially in sulfonylurea or meglitinide poisoning.

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ANTICHOLINERGICS

INTRODUCTION

- Anticholinergic drugs toxicity is commonly encountered, and familiarity with the management of this syndrome is essential. Discussion of specific agents that can cause an anticholinergic toxidrome and the general approach to the poisoned patient are found separately (See General Toxicology section P. 10)

SUBSTANCES POSSESSING ANTICHOLINERGIC PROPERTIES

CLASS	EXAMPLES
Antihistamines	Chlorpheniramine, Cyproheptadine, Doxylamine, Hydroxyzine, Diphenhydramine, Meclizine, Promethazine.
Neuroleptics	Chlorpromazine, Clozapine, Mesoridazine, Olanzapine, Quetiapine, Thioridazine.
Tricyclic antidepressants	Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin, Imipramine, Nortriptyline.
Antiparkinsonian drugs	Trihexyphenidyl, Benztropine.
Ophthalmic drugs	Atropine, Cyclopentolate.
Antispasmodics	Clidinium, Dicyclomine, Hyoscyamine, Oxybutynin, Propantheline.
Plants	Jimson Weed (Datura stramonium), Deady Nightshade (Atropa belladonna), Henbane (Hyoscyamus niger).

CLINICAL FEATURES:

Anticholinergic toxicity is almost always a clinical diagnosis

Manifestations of anticholinergic toxicity include:

- Flushing due to cutaneous vasodilation ("red as a beet").
- Anhydrosis ("dry as a bone").
- Hyperthermia due to loss of sweating ("hot as a hare").
- Blurry vision due to nonreactive mydriasis and paralysis of accommodation ("blind as a bat").
- Agitated delirium ("mad as a hatter").
- Urinary retention ("full as a flask").

- Decreased bowel sounds (can cause paralytic ileus so be aware not to administer activated charcoal if suspected).
- Tachycardia.
- Dehydration.

INVESTIGATIONS:

Routine:

- Bed side RBS to exclude hypoglycemia.
- ABGs and Electrolytes (Na, K, Ca, Mg).
- BUN, Creatinine, ALT, AST, Creatine Kinase.
- Serum Paracetamol and Salicylates.
- EKG.
- Pregnancy test for females in childbearing period.

Specific:

- Confirm intake through blood screening for tricyclic antidepressants, neuroleptics and antihistamines.

TREATMENT:

Stabilization:

- Secure the airway, breathing, and circulation and proper safe restraining in patients with severe agitation and/or hallucinations.

Decontamination:

- Administer activated charcoal (1 gm/kg, maximum 50 gm) to patients with intact mental status or a secure airway and likely recent ingestion of an anticholinergic agent.

Antidote:

- Patients who manifest both peripheral and moderate central (moderate to severe agitation/delirium) anticholinergic toxicity, without contraindications to physostigmine should be treated with this medication; 0.5-2 mg (0.02 mg/kg IV, up to a maximum of 0.5 mg/dose in pediatric patients). Physostigmine should be given by slow IV push, over five minutes (after consulting with the regional poison control center).
- Treat agitation and seizures with benzodiazepines (e.g., Lorazepam 1-2 mg IV push; may repeat as needed)
- Some differentiating features between classes of drugs causing anticholinergic manifestations:

- Because so many classes of drugs and toxins have anticholinergic effects, clinicians must differentiate pure anticholinergic poisoning from poisonings in which anticholinergic toxicity represents only one aspect.
    1) Tricyclic antidepressants can produce anticholinergic effects.
        a) Occur soon after overdose.
        b) Quinidine-like effects (resulting in a prolonged QRS interval) and α -blockade (resulting in hypotension) are usually more prominent.
    2) Phenothiazines have modest anticholinergic effects, but their sedating and α -blocking properties (hypotension) tend to predominate.
    3) Although sympathomimetic drug overdose and serotonin syndrome may present with manifestations similar to anticholinergics such as, agitation, tachy-cardia, and hyperthermia. Yet, sympathomimetic overdose and serotonin syndrome generally cause diaphoresis, in contradistinction to anticholinergic overdose.
    4) In agitated, hyperthermic patients with altered mental status, salicylate overdose should also be considered.

COMMON PITFALL

- The administration of phenothiazines or butyrophenones (e.g., haloperidol) is contraindicated in managing agitation induced by anticholinergic substances.

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CARDIOPULMONARY MEDICATIONS

BETA-BLOCKERS

(β -BLOCKERS)

INTRODUCTION:

- Beta blockers are widely available and are mainly used for the treatment of heart failure, hypertension, arrhythmias, angina pectoris, migraine, and glaucoma. Many patients presenting with beta-blocker overdose will concurrently suffer from underlying cardiovascular diseases or will be taking other cardiac medications, both of which may aggravate beta-blocker overdose.

EPIDEMIOLOGY

- Beta blocker toxicity is uncommon.
- Toxic manifestations following exposure are typically mild to moderate, with death developing in cases including co-ingestants or large amount.

CAUSES

- Toxic exposure is usually intentional type.
- Child neglect or abuse should be considered if the patient is less than one year of age, suicide attempt if the patient is over six years of age.

RISK FACTORS

- Cases with hypersensitive reactive airways condition may develop bronchospasm even at therapeutic doses.
- Elderly patients and those with underlying cardiovascular pathological condition may be intolerant of hypotension.
- Seizures and hypoglycemia are more common presentation in pediatrics, particularly with propranolol exposure.

DRUG AND DISEASE INTERACTIONS

- Co-ingestion of calcium channel blocker or digitalis medication may worsen bradycardia, dysrhythmias, & hypotension toxic effects.
- Co-ingestion of other antihypertensives drugs may worsen hypotension toxic degree.

MECHANISM OF TOXICITY:

- The manifestations of beta blockers toxicity depend on the specific agent and dose involved. In addition to blocking beta-adrenergic receptors, three properties affect toxicity which include the following:

- Membrane stabilizing activity (MSA): (e.g., propranolol, acebutolol) inhibition of fast sodium channels of myocytes, which can result in a widened QRS interval.
- Lipophilicity: Beta blockers with high lipid solubility (e.g., propranolol) rapidly cross the blood-brain barrier into the CNS, predisposing to neurologic sequelae such as seizures and delirium.
- Intrinsic sympathomimetic activity (ISA): Several agents act as partial agonists at the beta receptor binding site. This results in less bradycardia and hypotension when administered in therapeutic and supratherapeutic doses.

CLINICAL MANIFESTATIONS:

Cardiac:

- Bradycardia and hypotension are the most commonly observed effects and in significant overdoses can result in severe myocardial depression and shock.
- Ventricular dysrhythmias are seen more frequently following propranolol and acebutolol.
- Other manifestations:
  - Effects of severe toxicity include mental status change, seizures, hypoglycemia, and bronchospasm.
  - Early recognition and prompt treatment of hypoglycemia is critical.

EKG findings

- Slowing of conduction velocity across the AV node, resulting in PR prolongation, slow automaticity within the SA node, resulting in bradycardia.
- QRS prolongation is more commonly seen in poisoning with beta blockers with membrane stabilizing activity.
- In severe poisoning, the electrocardiogram (EKG) can show any bradydysrhythmia, and can progress to asystole.

INVESTIGATIONS:

Routine:

- Liver function tests, BUN, creatinine and urine output to assess kidney perfusion.
- Blood glucose may be low. The presence of hypoglycemia in a non-diabetic patient may help to distinguish β blockers poisoning from poisoning by CCBs.

- EKG monitoring and serum electrolytes.
- Arterial blood gases or oximetry.
- Pregnancy test in all women of childbearing age.

Specific:

- Serum concentrations of most β-blockers can be measured, they cannot be obtained in time to be clinically useful.
- Blood glucose, serum electrolytes including calcium. If calcium is administered repeatedly, levels of calcium should be measured every 4-6 hrs if calcium is to be administered frequently.
- If a decision is made to administer insulin/glucose treatment regimen, glucose and K levels must be measured every 30 to 60 minutes.

DIFFERENTIAL DIAGNOSIS:

- Other classes of antihypertensive or antidysrhythmic drugs (e.g. CCBs, β-blockers, digoxin, and clonidine).
- CCB toxicity is more frequentlty associated with hyperglycemia, while β-blockers toxicity is associated with hypoglycemia.
- Nausea and vomiting are more commonly observed with digoxin toxicity than β-blocker toxicity. Digoxin toxicity could result in a scooped ST segment depression on the EKG.
- Cholinergic agents toxicity present with bradycardia but also includes other characteristic features (DUMBBLES)

TREATMENT

Stabilization:

- Assess airway, breathing, and circulation and stabilize as necessary.
- Control hypotension and bradycardia: Administer boluses of isotonic IV fluids: Give atropine 1 mg IV (up to 3 doses)

Decontamination:

- Single-dose activated charcoal; whole bowel irrigation should be considered if the patient ingested extended-release preparation.

Specific therapy: for severe poisoning (e.g., profound hypotension)

- Glucagon: Administer 5 mg IV bolus (if the initial IV fluids and atropine were ineffective). Glucagon may be repeated if the initial bolus was ineffective.
- Calcium chloride (via central venous access): 10-20 mL of 10 % solution or calcium gluconate IV 30-60 mL of 10 % solution
- Vasopressors (e.g., epinephrine) can be used for hypotension

- High-dose insulin and glucose: Administer a bolus of 1 unit/kg IV of regular, short-acting insulin, followed by continuous infusion of 0.5 unit/kg/hour IV. The infusion rate can be increased until hypotension is corrected or dose becomes 2 units/kg/hour.
- Intravenous lipid emulsion (20 % solution): Give 1.5 mL/kg over 2 minutes, followed by 1.5 mL/kg infusion over 60 minutes.

Other potential treatments include:

- Sodium bicarbonate (e.g., prolonged QRS complex), magnesium (ventricular dysrhythmia),
- Consult the cardiologist to consider intraaortic balloon pump and/or temporary transvenous pacing.
- Hemodialysis has a minimal role in the treatment of β-blocker overdose and is effective only with hydrophilic, minimally protein-bound β-blockers. Hemodiyalysis could be effective with drugs like nadolol, sotalol, acebutolol, and atenolol but not with metoprolol, propranolol, and timolol.

FOLLOW UP:

- **PATIENT MONITORING**
  - Continuous close cardiac and hemodynamic monitoring.
  - Serum glucose in diabetics and pediatrics.
  - Pulmonary condition in patients with reactive hypersensitive airways status.
- **EXPECTED COURSE AND PROGNOSIS**
  - Most cases do well with gastrointestinal decontamination procedure and supportive care maneuver. Factors producing greatest risk for complications include:
    - Advanced age
    - Underlying pathological conditions (especially cardiovascular)
    - Co-ingestion of other cardiac depressant drugs (calcium channel blockers, digitalis, clonidine, etc.)
    - Massive amount of ingestion of sustained release preparation.
- **DISCHARGE CRITERIA/INSTRUCTIONS**
  - From the emergency department. Patients who have ingested an immediate-release formulation and are asymptomatic other than mild bradycardia may be discharged after gastric decontamination

procedure, a six-hour observation period, and psychiatric assessment, if required.

- From the hospital. Patients may be discharged following gastrointestinal decontamination procedure, recovery of cardiac manifestations, and psychiatric assessment, if required.

- **PATIENT EDUCATION**
  - Patients should be instructed carefully on usage and dosage of ophthalmic formulations.
  - Patients should be warned to avoid simultaneous use of beta-blockers and other drugs with similar actions (calcium channel blocker, digitalis) when possible.

COMMON PITFALLS

- Failure to determine whether the drug ingested was an immediate or extended release formulation, potentially leading to inappropriate treatment and disposition decision. Failure to check Finger stick glucose as β-blockers can cause hypoglycemia.
- Lack of appreciation that β-blockers with membrane stabilizing activity can cause delayed repolarization, cardiac conductive disorders (widened QRS) and ventricular tachyarrhythmias.
- Failure to anticipate seizures with lipophilic β-blockers such as propranolol.
- Failure to appreciate that sotalol has potassium channel blocking effects and can cause a prolonged QT interval and torsade de pointes.
- Failures to appreciate that severe poisoning are likely to require invasive monitoring, multiple pharmacological treatment, and mechanical hemodynamic support.

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CALCIUM CHANNEL BLOCKERS

INTRODUCTION:

- Calcium channel blockers (CCBs) are used widely in the management of angina pectoris, hypertension, cardiac arrhythmias, and other disorders. They are available in both rapid-release and extended-release preparations. The latter are more widely used clinically. Patients can develop severe signs of toxicity if they ingest more than 5 to 10 times the usual dose. Overdoses of CCBs could frequently result in life-threatening conditions.

TOXIC DOSE

- Ingestion of a gram or more of verapamil, nifedipine, or diltiazem can develop serious poisoning and possible death in an adult.
- The other preparations in this class appear less toxic, but few data are available on overdose exposure.

EPIDEMIOLOGY

- Calcium channel blocker toxicity is uncommon
- Toxic manifestations following exposure are typically mild to moderate.
- Death occurs in cases involving co-ingestants or a massive overdose exposure.

CAUSES

- Toxic ingestion is usually intentional type.

RISK FACTORS

- Elderly patients and those with underlying cardiovascular pathological may be intolerant of even mild hypotensive toxic effect.

DRUG AND DISEASE INTERACTIONS

- Hepatic impairment decreases CCB hepatic elimination.
- Co-ingestion of beta-blockers, digitalis, or class I antidysrhythmic medications may worsen bradycardia, dysrhythmias, and hypotension.
- Co-ingestion of other antihypertensives medications may worsen hypotension.

MECHANISM OF TOXICITY:

- CCBs attenuate the influx of calcium through cellular calcium channels. They mainly act on vascular smooth muscles and the heart. Additionally, they produce coronary and peripheral vasodilation, reduce cardiac contractility, slow (AV) nodal conduction, and suppress sinus node activity.

CCBs are divided into two major categories:

- **Dihydropyridines**, preferentially affect the vasculature such as nifedipine and amlodipine. They are potent vasodilators that have little negative effect upon cardiac contractility or conduction at therapeutic dosages.
- **Non-dihydropyridines**, such as verapamil and diltiazem are more selective towards the myocardium and they are weak vasodilators that negatively modulate cardiac conduction and contractility.
- Dihydropyridine intoxication results in arterial vasodilation and reflex tachycardia, whereas diltiazem and verapamil toxicity cause peripheral vasodilation reduced cardiac inotropy, and bradycardia. However, as the dose is increased, this selectivity can be lost, and dihydropyridine CCBs may affect the myocardium and conduction systems like verapamil and diltiazem.

CLINICAL MANIFESTATIONS:

Cardiac manifestations:

- Hypotension and bradycardia are often seen only in verapamil or diltiazem poisoning. However, bradycardia may also be seen with severe dihydropyridine poisoning.
- Jugular venous distension and other signs of heart failure may be noted in some cases.

Non-cardiac manifestations:

- Nausea and vomiting, abnormal mental status (stupor and confusion), and metabolic acidosis (probably resulting from hypotension).
- Reduced insulin release leads to hyperglycemia.
- Noncardiogenic pulmonary edema (NCPE) from increased transcapillary hydrostatic pressure.

INVESTIGATIONS:

Routine:

- Liver function tests, BUN, and creatinine, as well as urine output to assess renal perfusion.
- Blood glucose measurement may reveal hyperglycemia, which is caused by inhibition of calcium-mediated insulin release; however, this elevation is rarely clinically significant, except for diagnostic purposes. The presence of hyperglycemia in a non-diabetic patient may help to distinguish CCB from β-blocker poisoning.

- Serum electrolytes including calcium should be assessed.
- Arterial blood gases or oximetry, and EKG monitoring
- Pregnancy test in all women of childbearing age.

Specific:

- Serum drug levels are not widely available. Detection of diltiazem and verapamil is possible using comprehensive urine toxicology screening.

TREATMENT

Stabilization:

- Assess airway, breathing, and circulation and stabilize as necessary
- Monitor the vital signs and EKG for at least 6 hrs after an alleged ingestion.

Decontamination:

- Single-dose activated charcoal. Consider whole bowel irrigation if an extended-release preparation has been ingested.

Treatment of hypotension and bradycardia:

- Intravenous crystalloid (hypotension): Isotonic saline 500-1000 mL boluses.
- Atropine (bradycardia): 1 mg IV (0.02 mg/kg in children); may repeat for 3 total doses.
- For patients with severe CCB poisoning (e.g., profound hypotension refractory to crystalloid boluses and atropine), give multiple simultaneous interventions, including all of the following: Calcium salts, glucagon, high-dose insulin and dextrose, vasopressors & lipid emulsion therapy.

Specific therapy:

Intravenous calcium (hypotension and/or bradycardia)

- **Bolus therapy:**
  - Calcium chloride – 10-20 mL of 10 % solution (via central venous access if possible)
  - Calcium gluconate – 30-60 mL of 10 % solution.
  - Continuous infusion of 0.5 mEq calcium/kg/hour.
  - Monitor serum calcium and EKG for evidence of hypercalcemia.

Glucagon (bradycardia)

- **Bolus therapy:**
  - Glucagon 1-5 mg IV push, may repeat up to 15 mg total.

- **Continuous infusion:**
  - Determine the bolus amount needed to obtain response; administer this "response dose" every hour as a continuous infusion.

Vasopressor support (hypotension)

- Norepinephrine: begin 2 µg/minute IV, titrate rapidly to systolic blood pressure 100 mmHg

Hyperinsulinemia with euglycemia (HIE) therapy (hypotension)

- Relative hypoglycemia and hypokalemia must be corrected prior to initiating high-dose insulin therapy.

Bolus therapy:

- Regular insulin 1 unit/kg IV
- Dextrose 25-50 gm IV; repeat for hypoglycemia; give potassium for hypokalemia.

Maintenance infusions:

- Regular insulin: Start infusion at 0.5 unit/kg/hour IV; titrate upwards until hypotension is corrected or maximum dose of 2 units/kg/hr is reached.
- Dextrose 0.5 gram/kg per hour; titrate to euglycemia.

Lipid emulsion

- Lipid emulsion to patients with hypotension refractory to other therapies. Administer 1.5 mL/kg of 20% lipid emulsion over 2-3 minutes as an IV bolus, followed by an infusion of 0.25 mL/kg/min. If possible, discontinue after 30-60 minutes.
- If the above measures fail, consult the cardiologist to consider the following:
  - Transvenous cardiac pacing
  - Intraaortic balloon pump
  - Cardiopulmonary bypass
  - Extracorporeal membrane oxygenation

PATIENT MONITORING

- Continuous respiratory, cardiac, and hemodynamic close monitoring should be instructed.
- Serum glucose should be frequent monitored in diabetics and pediatrics.

EXPECTED COURSE AND PROGNOSIS

- Most patients do well with gastrointestinal decontamination and supportive care.
- Course may be prolonged and complicated in cases with massive ingestion, advanced age, underlying cardiovascular pathological condition, or co-ingestion of other cardiac depressant drugs.
- Sequelae of prolonged toxic hypotensive effect may develop in severe toxic cases.

DISCHARGE CRITERIA/INSTRUCTIONS

- From the emergency department. Asymptomatic cases may be discharged following gastric decontamination maneuver, six hours of close observation, and psychiatric assessment, if needed. Ingestion of a sustained-release preparation usually warrants 24-hours close observation.
- From the hospital. Patients may be discharged following gastrointestinal decontamination procedure, recovery of cardiac toxic effects, and psychiatric assessment, if required.

COMMON PITFALLS

- Failure to consider CCB poisoning in patients with hypotension, bradycardia or AV block, particularly when hyperglycemia is present.
- Failure to appreciate that ingestion of single pill may be lethal in a toddler.
- Failure to consider whole bowel irrigation or multiple doses activated charcoal for patients with overdoses of extended-release preparations.
- Failure to initiate HIE therapy in a timely manner.

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CARDIAC GLYCOSIDES

INTRODUCTION:

Cardiac glycosides affect the heart and they are recognized by presence of a common steroid nucleus at the heart of these drugs. The most common product is digoxin. Other preparations include digitoxin, ouabain, lanatoside C, deslanoside, and gitaline. Both digoxin and digitoxin have a narrow therapeutic index and toxicity is common.

TOXIC DOSE

Ingestion of greater than 10 mg digoxin by an adult or more than 4 mg by a child has been fatal.

EPIDEMIOLOGY

- Digoxin toxicity is uncommon.
- Toxic manifestations following exposure are typically mild degree.
- Death develops in cases with unrecognized digoxin toxicity.

CAUSES

- Poisoning usually results from suicidal attempt.

RISK FACTORS

- Underlying cardiac pathological condition may predispose to dysrhythmia.
- The elderly require smaller amount of digitalis and are more likely to have an underlying disease that predisposes to toxicity.

DRUG AND DISEASE INTERACTIONS

- Concurrent use of other drugs (beta-blocker, calcium channel blocker) can cause severe bradycardia or more conduction delay.
- Quinidine, quinine, verapamil, diltiazem, amiodarone, erythromycin, and tetracycline may rise digoxin levels.
- Nifedipine, spironolactone, triamterene, and amiloride decrease renal clearance of digoxin.
- Warfarin can increase free digoxin level in the blood
- Renal impairment depresses digitalis elimination.
- Hepatic failure depresses digitoxin elimination.
- Hypokalemia, hypercalcemia, hypomagnesemia, induce sympathetic system activity, and hypothyroidism may augment digitalis toxicity.

MECHANISM OF TOXICITY:

- Inhibition of the Na-K ATPase-dependent myocardial sarcolemmal pump. The increase in intracellular sodium prevents the sodium-calcium

transporter from pushing calcium outside the myocyte, which increases intracellular calcium and augments inotropy

- The increase in intracellular calcium may lead to premature contractions and stimulate arrhythmias. Cardiac glycosides shorten repolarization of the atria and ventricles, reducing the refractory period of the myocardium, thereby increasing automaticity and the risk for arrhythmias.
- The increase in vagal tone results in decreased conduction through the sinoatrial and atrioventricular nodes.
- Peripheral vasodilation and reduced afterload.

CLINICAL MANIFESTATIONS:

Non-cardiac manifestations:

Acute Toxicity:

- Following an asymptomatic period of several minutes to several hours, the first set of symptoms are usually anorexia, nausea, vomiting, or abdominal pain.
- CNS: Lethargy, confusion, and weakness that are not caused by hemodynamic changes.

Chronic Toxicity:

- Chronic toxicity is often difficult to identify due to its slow development.
- Symptoms may include those with acute poisonings; however, they are often less obvious.
- Gastrointestinal symptoms, as well as delirium, confusion, disorientation, drowsiness, headache.
- Visual changes may include experiencing yellow halos around light, scotomas, blindness, hallucinations and seizures may rarely occur.

Cardiac manifestations:

- Digoxin toxicity can produce bradycardia, heart block, different types of cardiac arrhythmias that may evolve and change rapidly. Thus, performing continuous cardiac monitoring and obtaining serial electrocardiograms (EKG) is important in the setting of toxicity.

Acute Toxicity:

- The initial increased vagal tone at the sinoatrial (SA) and atrioventricular (AV) nodes results in a bradydysrhythmia that is responsive to atropine.

Chronic Toxicity:

- Ventricular tachydysrhythmias are more common in patients with chronic or late acute poisoning than they are in early acute poisoning.

DIFFERENTIAL DIAGNOSIS:

Toxicologic:

- Poisoning with β-blockers, calcium channel blockers, and α-agonists (e.g., clonidine) can present with bradycardia and hypotension being prominent features. (Clonidine poisoning leads to greater CNS depression, respiratory depression, and miosis).

Non-toxicologic:

- Hypothermia, hypothyroidism, myocardial infarction, and hyperkalemia from other causes.

INVESTIGATIONS:

Routine:

- Liver function tests, BUN, creatinine and urine output to assess kidney perfusion.
- Blood glucose to rule out hypoglycemia.
- Serum electrolytes.
- Arterial blood gases or oximetry.
- EKG monitoring.
- Pregnancy test in all women of childbearing age.

Specific:

Serum digoxin concentration

- It does not necessarily correlate with toxicity, but may be used in some cases to determine the dosing of antidotal therapy with Fab fragments.
- Following the administration of Fab fragments, serum immunoassays of digoxin are unreliable as they measure both bound and unbound drug. Fab treatment frequently causes an elevation in the measured digoxin concentration despite a free digoxin level approaching zero. The measurement of "free" digoxin

concentrations may be helpful in determining when a patient can restart digoxin, if desired.

N.B. Elevated digoxin levels have been identified in pregnant women, newborns, and patients with acromegaly, subarachnoid hemorrhage, liver disease, and renal failure due to endogenous digoxin-like substances.

Electrolyte abnormalities

Serum potassium concentration

- Inhibition of Na-K-ATPase in both heart and skeletal muscles, leads to an increase in extracellular potassium. Therefore, hyperkalemia is an important indicator of acute digitalis toxicity. It is a better predictor of lethality than either the initial EKG changes or the serum digoxin concentration. (K > 5.5 mEq/L is a poor prognostic sign). Note that simply correcting the hyperkalemia does not increase patient survival; it is a marker of, and not the cause of, the morbidity and mortality
- In chronic toxicity, hypokalemia is of greater concern. Several electrolyte abnormalities, including hypokalemia, hypomagnesemia and hypercalcemia, increase patient susceptibility to the toxic effects of digoxin.

TREATMENT:

Stabilization:

- Assess airway, breathing, and circulation; stabilize as necessary
- Continuous cardiac and pulse oximetry monitors
- EKG monitoring.
- The treatment for any clinically significant arrhythmia from digitalis toxicity, such as those producing hypotension with digoxin -specific antibody (Fab) fragments.
- With the availability of digoxin - specific antibody (Fab) fragments antibodies, all other therapies are considered equivocal.

Decontamination:

- Activated charcoal should be given within 1-2 hrs of digoxin ingestion to patients who can protect their airway and are not actively vomiting. Repeated doses of activated charcoal administration (1 gm/kg/2–4 hrs for up to 4 doses) may assist in reducing serum concentration.

Antidote:

- Antidotal therapy with antibody (Fab) fragments
  - Early recognition of digitalis toxicity and prompt administration of Fab fragments is essential for the successful treatment of severe poisoning.
  - Fab fragments are highly effective and safe and have transformed the management of cardiac glycoside poisoning.
- Recommendations for administration of digitalis antibody fragments:
  - Life-threatening or hemodynamically unstable arrhythmia (e.g., ventricular tachycardia,+++ VF, asystole, complete heart block, Mobitz II heart block, symptomatic bradycardia)
  - Hyperkalemia (serum potassium >5-5.5 mEq/L [>5-5.5 mmol/L])
  - Evidence of end-organ dysfunction from hypoperfusion (e.g., renal failure, altered mental status)
  - Serum digoxin level is > 10 ng/mL (13 nmol/L) in acute ingestions, or > 4 ng/mL (5.1 nmol/L) in chronic ingestions
  - Intake of more than 10 mg or a child more than 4 mg acutely.
- Calculating the dose of fab fragments:

  Acute digoxin toxicity:
  - If the digoxin level or amount ingested is known, administer empiric doses of 10 vials of Fab fragments which should be repeated if clinical response is inadequate. Children can be adequately treated with 5 vials and the dose can increase based on clinical response.
  - Amount of digoxin ingested is known but concentration is unknown
    - No. of vials = Amount ingested (mg) × 0.8 ÷ 0.5
  - Steady state digoxin concentration is known
    - No. of vials = Serum Digoxin (ng/mL) × Pt Wt (kg) ÷ 100

  Chronic digoxin toxicity:
  - Patients with acute symptoms and without known serum digoxin concentration:
  - Administer empiric doses of 6 vials (240 mg) of Fab fragments for adults and older/larger pediatric patients.

  If steady state digoxin concentration is known:

- No. of vials = Serum Digoxin (ng/mL) × Pt Wt (kg) ÷ 100

Chronic toxicity without severe signs:

- Chronic toxicity without manifestation of acutely life-threatening arrhythmias (e.g., AV nodal blockade present on EKG but patient maintains normal blood pressure and stable mental status), half the recommended dose can be given initially as administration of a full dose can result in acute decompensated heart failure or atrial fibrillation with rapid ventricular response.

Supportive:

- A serum K level > 5 mEq/L warrants consideration of Fab treatment. If Fab fragments are not immediately available, severe hyperkalemia should be managed using IV glucose, insulin, and sodium bicarbonate.
- If Fab fragments are not immediately available, symptomatic bradycardia or bradyarrhythmia can be managed with atropine. (0.5 mg IV in adults; 0.02 mg/kg IV in children, minimum dose 0.1 mg) and hypotension with IV boluses of isotonic crystalloid. Life-threatening ventricular arrhythmias are treated according to the algorithms of advanced cardiac life support.

PATIENT MONITORING

- Continuous close cardiac and hemodynamic monitoring should be instituted and serum potassium level followed closely.
- Recovery is usually complete, but often complicated by patient's underlying pathological condition.
- Sequelae of hypotensive or hypoxic effects may occur.

EXPECTED COURSE AND PROGNOSIS

- Improvement within 30 minutes of digoxin Fab treatment is predicted if complications of shock, hypoxia, or a coingestant have not developed.

DISCHARGE CRITERIA AND INSTRUCTIONS

- From the emergency department. Asymptomatic cases with nontoxic digoxin level, normal EKG, and normal electrolytes levels may be discharged following gastrointestinal decontamination procedures, six hours of close observation, and psychiatric assessment, if required.

- From the hospital. Patients may be discharged following gastrointestinal decontamination procedure, recovery of cardiac toxic manifestations, and psychiatric assessment, if required.

COMMON PITFALLS

- Failure to appreciate that signs of toxicity may be delayed up to 8 hrs after acute ingestion.
- Digoxin has a slow redistribution phase, so high serum concentrations are expected for several hours following doses. A single high digoxin concentration in an otherwise asymptomatic patient is not an indication for treatment.
- Failure to appreciate that digoxin assays may not yield a measurable digoxin level with ingestion of cardiac glycosides from plants.
- Failure to appreciate that difference between acute and chronic cardiac glycosides poisoning.

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THEOPHYLLINE

INTRODUCTION:

- Theophylline has been widely used as a bronchodilator for the treatment asthma and COPD and is commonly used to treat neonatal apnea in preterm infants.
- The incidence of poisoning has significantly declined in recent years due to the decrease in prescribing theophylline for asthmatic patients. Theophylline poisoning is uncommon, but serious toxicity and deaths are reported every year.

TOXIC DOSE:

- The manifestations of acute toxicity (e.g., vomiting) may occur with low dose as 7.5 mg/kg. Theophylline has a narrow therapeutic index.

EPIDEMIOLOGY:

- Theophylline toxicity is uncommon
- Toxic manifestations following exposure are typically mild to moderate after acute overdose and moderate to severe after chronic overdose
- Death is more likely after chronic theophylline overdose and in pediatrics or the elderly patients.

CAUSES:

- Excessive therapeutic dosing is the most common pattern of toxicity; serum theophylline levels should be monitored closely when rising maintenance theophylline dose.
- Decreased metabolism leading to elevated serum theophylline levels may result from drug interactions, alcoholic liver impairment, and congestive heart failure.
- Chronic theophylline overdose is usually accidental exposure, iatrogenic errors, or the result of medication interactions.
- Acute theophylline overdose is usually a non-accidental incident in adults and accidental in pediatrics.
- Child abuse should be considered if the patient is less than one year of age; suicide attempt if the patient is more than six years of age

RISK FACTORS:

- Cases over 60 or under three years of age are at highest risk for severe complications (dysrhythmia, seizure) after chronic overdose.
- Hepatic dysfunction may predispose a patient to theophylline toxicity.

DRUG AND DISEASE INTERACTIONS:

- Many medications decrease the rate of theophylline metabolism and may cause intoxication: allopurinol, cimetidine, ciprofloxacin, clarithromycin, disulfiram, pentoxifylline, pipenidic acid, propafenone, propranolol, tacrine, thiabendazole, enoxacin, erythromycin, ethanol, estrogen, idrocilamide, interferon A, methotrexate, mexiletine, norfloxacin, ofloxacin, pefloxacin, ticlopidine, troleandomycin, and verapamil.

MECHANISM OF TOXICITY:

- Pharmacology: It inhibits phosphodiesterase, which in an increase in cyclic adenine monophosphate and catecholamine release, and is also an antagonist at the adenosine receptor site.
- Toxicology: Increase catecholamine levels (epinephrine and norepinephrine) cause tachycardia, hypotension, anxiety, and hyperglycemia. Adenosine receptor antagonism may cause seizures.

CLINICAL MANIFESTATIONS:

- Mild to moderate toxicity:

  Nausea, vomiting, abdominal pain, sinus tachycardia, sustained complex atrial or ventricular ectopy, tremor, agitation, hypokalemia, hyperglycemia, hypophosphatemia, and hypercalcemia can develop.
- Severe toxicity:

  Seizures, rhabdomyolysis, hypotension, and ventricular dysrhythmias can occur.
- Chronic overdose:

  GIT symptoms may be absent. Severe effects, such as seizures and significant dysrhythmias, are more common with chronic overdoses than with acute overdoses. The onset of symptoms may occur abruptly.
- Evaluation and clinical assessment:
  - CNS: Agitation, hyperventilation, headache and convulsions.
  - CVS: Pulse (rate, rhythm) for tachycardia and arrhythmias and blood pressure.
  - GIT: Nausea & vomiting (may be bloody), abdominal pain, thirst, diarrhea.

DIFFERENTIAL DIAGNOSIS:

- Theophylline toxicity should be considered in any patient presenting with seizures, agitation, tachyarrhythmias, hypotension, or persistent vomiting, particularly if there is hypokalemia and hyperglycemia. However, patients with chronic intoxication may present with few overt symptoms. Other toxic agents to consider in patients with these symptoms include: β 2 adrenergic agonists, cocaine, amphetamine, iron and salicylates.

INVESTIGATIONS:

Routine:

- Monitor serum glucose, serum electrolytes, and ABGs.
- Monitor CPK levels and renal function in patients with seizures. Institute continuous cardiac monitoring and obtain an EKG.
- Paracetamol and salicylate levels.
- Pregnancy test in all women of childbearing age.

Specific:

- Serum theophylline concentrations.
    - Serial theophylline levels are required at 2 hrs then every 2 hrs until peak levels are reached or start to decline.
    - If a slow release preparation has been ingested, continue measuring levels at 4 hrs intervals after decline or plateau to ensure detection of a secondary peak.
    - Therapeutic serum levels: The therapeutic steady-state serum concentration for theophylline ranges from 10-20 µg/mL (56-111 µmol/L).
    - Morbidity correlates with serum theophylline concentration in patients with acute toxicity but not in patients with chronic toxicity.

ADMISSION CRITERIA:

- Admit all patients with:
    - Acute ingestion of > 10 mg/kg.
    - Chronic intoxication.
    - Ingestion of slow release preparations.
    - Any ingestion while on a maintenance dose of theophylline.
    - Ingestion of an unknown quantity.
    - All symptomatic patients.

Because of the potential for severe toxicity, most patients should be considered for admission to an intensive care setting.

TREATMENT:

Stabilization:

- ABCs: airway, breathing, and circulation (ABC) should be evaluated and stabilized.
- Control vomiting by metoclopramide intravenously (initial dose 0.1 mg/kg up to 20 mg) may be used in addition to ondansetron (initial dose: 0.15 mg/kg up to 12 mg intravenously) + H2 blocker or proton pump inhibitors.

Decontamination:

- Activated charcoal 1gm/kg initially unless altered conscious state (protect airway first) then 0.5gm/kg/ 4 hourly.
- Whole bowel irrigation (WBI) is not routinely used but can be considered for massive ingestions of sustained preparation or enteric-coated drugs in an alert and cooperative patient.

Supportive treatment:

- Hypotension: Initial treatment for hypotension consists of a rapid infusion of isotonic saline (initial dose: 20 mL/kg, up to 1 L) and treatment of any cardiac arrhythmias. If hypotension does not respond to fluid administration and/or treatment of cardiac arrhythmias, a pure α-adrenergic agonist (such as phenylephrine) or a predominant α-adrenergic agonist (such as norepinephrine) should be used.
- Cardiac arrhythmias should be treated according to ACLS or PACLS. Esmolol is safe for use in theophylline-poisoned patients with asthma and has also been used effectively to terminate supraventricular tachycardia. In children, the dose is 100-500 µg/kg, IV, given over 1min. In adults, rapid IV infusion of 500 µg/kg over 1min is followed by a continuous infusion of 50 µg/kg infusion for at least 4 min.
- If the patient has a depressed level of consciousness, arrhythmias or intractable vomiting, the patient may be in a need for intubation.
- For Agitation and seizures administer benzodiazepines (e.g., lorazepam 0.1 mg/kg, repeat in 1-2 minutes if seizures continue) or phenobarbitone (20 mg/kg, maximum initial dose: 1 gm). Phenytoin should be avoided in all patients with theophylline toxicity.

- Potassium supplementation (e.g., 40 mEq of KCL/L in intravenous fluids run at 1-1.5 times maintenance) for hypokalemic theophylline poisoned patients with potassium <3 mEq/L or with ventricular arrhythmias.
- Metabolic acidosis after theophylline poisoning rarely requires specific intervention (e.g., administration of sodium bicarbonate), unless severe (e.g., pH < 7.0).

Elimination Enhancement:

Haemodialysis:

Indications for hemodialysis:

In acute overdose:

- Patients with seizures or significant cardiac arrhythmias (e.g., ventricular tachycardia).
- Peak theophylline level: ≥ 80 µg/mL (448 µmol/L).
- Peak theophylline level: ≥ 60 µg/mL (336 µmol/L) with any of the following comorbidities:
    - Inability to tolerate multiple-dose activated charcoal (e.g., intractable vomiting, gastrointestinal ileus or obstruction).
    - Impaired theophylline metabolism (e.g., liver disease, heart failure).
    - High risk for seizures or history of epilepsy (see 'Seizures' above).
    - Increased susceptibility to toxicity including age > 65 years or < 6 months, ischemic heart disease, and/or severe chronic lung disease.

In chronic overdose:

- Any patient who has already experienced a significant arrhythmias or seizures.
- If the plasma theophylline concentration approaches 40-60 µg/mL.
- Infants < 6 months old or adults > 65 years of age.
- Theophylline levels of 30-40 µg/mL (168-224 µmol/L).

N.B. For asymptomatic patients: Administer activated charcoal 1gm/kg and observe for 4 hrs. If no symptoms appear, the patient did not ingest

slow release preparation and serum theophylline levels are < 20 µg/mL, the patient can be discharged.

FOLLOW UP:

PATIENT MONITORING

- Serial serum theophylline level should be monitored every 2-4 hours until it decreases and patient clinically improves.
- An EKG should be recorded and continuous close cardiac monitoring instructed.
- Serum electrolytes levels should be close monitored daily, more often during acute intoxication as ordered.

EXPECTED COURSE AND PROGNOSIS

- Acute intoxication
  - Patients generally do well with adequate gastrointestinal decontamination procedures and multiple-dose activated charcoal administration.
  - Effects usually peak in the first 12-hours and then subside.
  - Toxicity onset may be delayed or prolonged after oral intake of sustained-release preparation.
- Chronic intoxication
  - There is a high risk of complications and death than with acute theophylline intoxication, especially for patients over 60 or under three years of age and those with significant underlying pathological conditions.
  - Aggressive treatment with early hemodialysis may improve the outcome in these cases.
  - Possible sequelae involve neurologic impairment from intractable seizures, dysrhythmia, or toxic hypotension.
  - Intestinal obstruction, paralytic ileus, and severe constipation from multiple-dose activated charcoal may be life threatening.
  - Severe myocardial ischemia may develop from increased oxygen demand.

DISCHARGE CRITERIA/INSTRUCTIONS

From the Emergency Department

- Patients may be discharged when:
  - Serum levels decrease below 25 µg/mL.
  - Manifestations of intoxications are recovered.
  - Psychiatric assessment, if required, has been done.
- All drugs should be reviewed before patient discharge to avoid recurrent drug interactions.

From the Hospital

- Patients may be discharged when:
  - Serum levels decrease below 25 µg/mL.
  - Manifestations of intoxications are recovered.
  - Patient is passing activated charcoal stool.
  - Psychiatric assessment, if required, has been done.
- All drugs should be reviewed before patient discharge to avoid recurrent drug interactions.

PATIENT EDUCATION:

- Patients should be educated about risk of drug interactions and the dangers of increasing theophylline dosage without monitoring serum theophylline levels.

COMMON PITFALLS:

- Selective β-adrenergic agonists (such as dobutamine) and mixed α - β adrenergic agonists (such as epinephrine) should not be used.
- The control of nausea and vomiting with an antiemetic and the early administration of activated charcoal is very important in order to prevent further absorption and enhance elimination of theophylline.
- Patients who have ingested sustained-release formulations may not develop peak serum concentrations for 24 hours.
- Patients with chronic toxicity may develop severe clinical effects abruptly.

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PSYCHOTROPIC MEDICATIONS

LITHIUM

INTRODUCTION:

- Lithium carbonate was approved in the United States for the treatment of acute mania and bipolar disorder. Lithium has a relatively narrow therapeutic index. A significant proportion of patients on chronic lithium therapy experience at least one episode of toxicity during treatment. Lithium is found to accumulate intracellularly in the brain and the kidneys. Elderly patients are at higher risk for lithium toxicity due to both a lower glomerular filtration rate and a reduced volume of distribution.

MECHANISM OF TOXICITY:

- Lithium is a naturally occurring metal that possesses chemical similarity to Na^+ and K^+. The specific mechanism by which it stabilizes mood is not known. It is thought to modulate the CNS by altering nerve conduction, cortisol and monoamine metabolism, and increasing serotonin.
- At the renal tubules, lithium was found to compete with Na^+ and K^+. Conditions that increase renal sodium reabsorption (dehydration) decrease lithium elimination.
- Chronic toxicity typically occurs as a result of medication interactions, renal impairment and in dehydrated patients due to decreased renal clearance.

CLINICAL MANIFESTATIONS:

Acute Toxicity:

- Early GI symptoms (nausea, vomiting, and diarrhea).
- Neurologic manifestations are a late finding. They include sluggishness, ataxia, confusion or agitation, and neuromuscular excitability, that can present as irregular coarse tremors, fasciculations, or myoclonic jerks. Severe lithium intoxication can lead to seizures, status epilepticus, and encephalopathy.
- EKG abnormalities: T-wave flattening or inversion, prolongation of the QTc, sinoatrial nodal dysfunction, and bradycardia may occur and malignant dysrhythmias.

Chronic Toxicity:

- Predominantly neurologic findings: Mental status is often altered and can progress from confusion to stupor, coma, and seizures. Tremor,

fasciculations, hyperreflexia, choreoathetotic movements, clonus, dysarthria, nystagmus, and ataxia may occur.

- Renal: Nephrogenic diabetes insipidus and a chronic tubulointerstitial nephropathy,
- Cardiac: Dangerous arrhythmias or other important clinical effects are rare. Flattened T waves, prolonged QTc intervals, and bradycardia.
- Endocrine disorders: Hypothyroidism and hyperparathyroidism and diabetes insipidus.
- Hematological: Leukocytosis and an increase in neutrophils and aplastic anemia.

Acute-on-Chronic Toxicity:

- Patients are at risk for signs and symptoms of both acute and chronic toxicity.

ADMISSION CRITERIA:

- Patients with symptoms of lithium toxicity are admitted to a monitored setting for observation, regardless of the serum lithium concentration.
- Patients with severe symptoms (e.g., altered mental status, seizures) are admitted to an intensive care setting.
- Discharge is appropriate once patients are asymptomatic with stabilization of serum lithium concentration below 1.5 mEq/L (1.5 mmol/L), spaced for 24 hrs and no rebound manifestations (disorientation, agitation or any neurological signs)

DIFFERENTIAL DIAGNOSIS:

- Extrapyramidal effects from other medications.
- Neuroleptic malignant syndrome and serotonin syndrome from other agents.
- Sepsis, CNS infections, or intracranial catastrophes (massive hemorrhage or stroke).

INVESTIGATIONS:

Routine:

- Monitor serum glucose, serum electrolytes (particularly sodium), urinalysis, serum BUN creatinine, ALT, AST, and WBC.
- ABG: lithium intoxication may cause a low anion gap.
- Screen for any co-ingestants (e.g., paracetamol and Salicylate levels).
- EKG (QT, T, ST wave's changes) and urine analysis and urine output.

- CT scan of the brain may be warranted if the etiology of altered mentation is not identified.
- Chest x-ray may be indicated to monitor pulmonary edema and in patients with worsening symptoms or known large ingestions.

Specific:

- Therapeutic serum lithium is 0.5-1.3 mmol/l. Serum lithium concentrations often do not correlate with clinical signs of toxicity in patients with acute ingestions. However, it correlates more closely with clinical signs in patients with chronic toxicity.
- Thyroid function tests.

TREATMENT:

Stabilization:

- Airway, breathing, and circulation (ABC) should be evaluated and stabilized as necessary.

Decontamination:

- Whole bowel irrigation with polyethylene glycol should be considered with a large ingestion or ingestion of a sustained-release product.
- Do not give activated charcoal as it is not effective.

Specific:

- Rehydrate the patient. Beware of existing renal insufficiency or congestive heart failure. Best IV fluids are normal saline. Do not attempt to eliminate lithium using diuretics.

Hemodialysis is indicated for:

- Acute over dose patients with level > 4 mEq/L.
- Chronic over dose patients with level > 2.5 mEq/L.
- Severe neurological signs such as stupor with level > 2.5 mEq/L.
- Patients with mild signs of toxicity and renal impairment.
- Patients who cannot tolerate rehydration (as CHF or arrhythmia).
    - Recheck lithium level immediately post-dialysis and importantly 6-12 hrs post-dialysis.
    - Request another hemodialysis session if lithium rises once again, or previous indications still exist.

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TRICYCLIC ANTIDEPRESSANTS

INTRODUCTION:

- Tricyclic antidepressants (TCAs) are still used for depression and other indications. Consequently, TCA poisoning, which can be life-threatening and remains a significant clinical issue. It is common for a patient to present to the emergency department with minimal clinical abnormalities and to then develop life-threatening cardiovascular and CNS toxicity within 2 hours. TCAs have a low toxicity threshold, so a small increase over the therapeutic range may result in toxicity.

MECHANISM OF TOXICITY:

- Inhibition of presynaptic neurotransmitter reuptake (norepinephrine and serotonin) is the primary mechanism for the therapeutic effects of tricyclic antidepressants (TCAs). Following acute overdose, the following molecular changes often lead to important clinical consequences:
  - Blockade of cardiac fast sodium channels.
  - Antagonism of central and α-1 adrenergic receptors.
  - Antagonism of histamine (H1) receptors.
  - Antagonism of CNS gamma-aminobutyric acid (GABA) A receptors.

CLINICAL MANIFESTATIONS:

Cardiac:

- Sinus tachycardia is common in TCA overdose, likely due to anticholinergic effects and hemodynamic decompensation causing a reflex tachycardia. Hypotension is common following significant TCA poisoning, and mortality from TCA overdose is due largely to refractory hypotension.
- Cardiac conduction abnormalities may contribute to hypotension.
- Ventricular tachycardia and ventricular fibrillation (VT and VF) are more common in severe poisonings (e.g., severe acidosis, hypotension), particularly those involving extreme QRS prolongation.

CNS manifestations:

- Mental status changes, such as a decreased level of consciousness (due to antihistaminic effects) or, less frequently, delirium (due to anticholinergic effects), are common following TCA overdose.
- TCA poisoning can cause seizures, likely due to the antagonistic effects of TCAs on the GABA-A receptor

Anticholinergic manifestations:

- TCAs have anticholinergic effects and signs such as hyperthermia, flushing, dilated pupils that respond poorly to light, delirium, intestinal ileus, and urinary retention.

INVESTIGATIONS:

Routine:

- Monitor serum glucose, serum electrolytes (particularly sodium), urinalysis, serum BUN creatinine, ALT, AST.
- Acetaminophen and salicylate levels.
- Urinalysis should be repeated in patients at risk for rhabdomyolysis.
- Serial ABG are performed in severe toxicity to monitor the acid-base status.
- Pregnancy test in all women of childbearing age.

Specific:

- Continuous cardiac monitoring for arrhythmias until the patient becomes free of any symptoms or signs of cardiac toxicity for at least 4hrs.
- EKG changes in severe TCAs poisoning include:
  - Prolongation of the QRS >100 msec.
  - Abnormal morphology of the QRS (e.g., deep, slurred S wave in leads I and AVL)
  - Abnormal size and ratio of the R and S waves in lead AVR: R wave in AVR > 3 mm; R to S ratio in AVR > 0.7
- Measurement of TCA concentrations:
  - Qualitative (urine) and quantitative (serum) TCA testing have limited therapeutic and prognostic utility in the acute setting.

DIFFERENTIAL DIAGNOSIS:

- Other agents with anticholinergic effects may produce a similar clinical appearance.

TREATMENT:

Stabilization:

- Assess airway, breathing, and circulation and stabilize as necessary.
- Because patients with TCA poisoning can deteriorate very rapidly, early intubation is advised for patients with CNS depression and/or hemodynamic instability.

- Monitor the vital signs and EKG for at least 6 hrs after alleged ingestion.

Decontamination:

- Administer activated charcoal if the patient presents within 2 hrs of ingestion unless gastrointestinal complications (ileus, obstruction) are suspected. Dose is 1 gm/kg (maximum dose 50 gm). The patient's ability to protect the airway or the need for intubation should be considered before using activated charcoal.

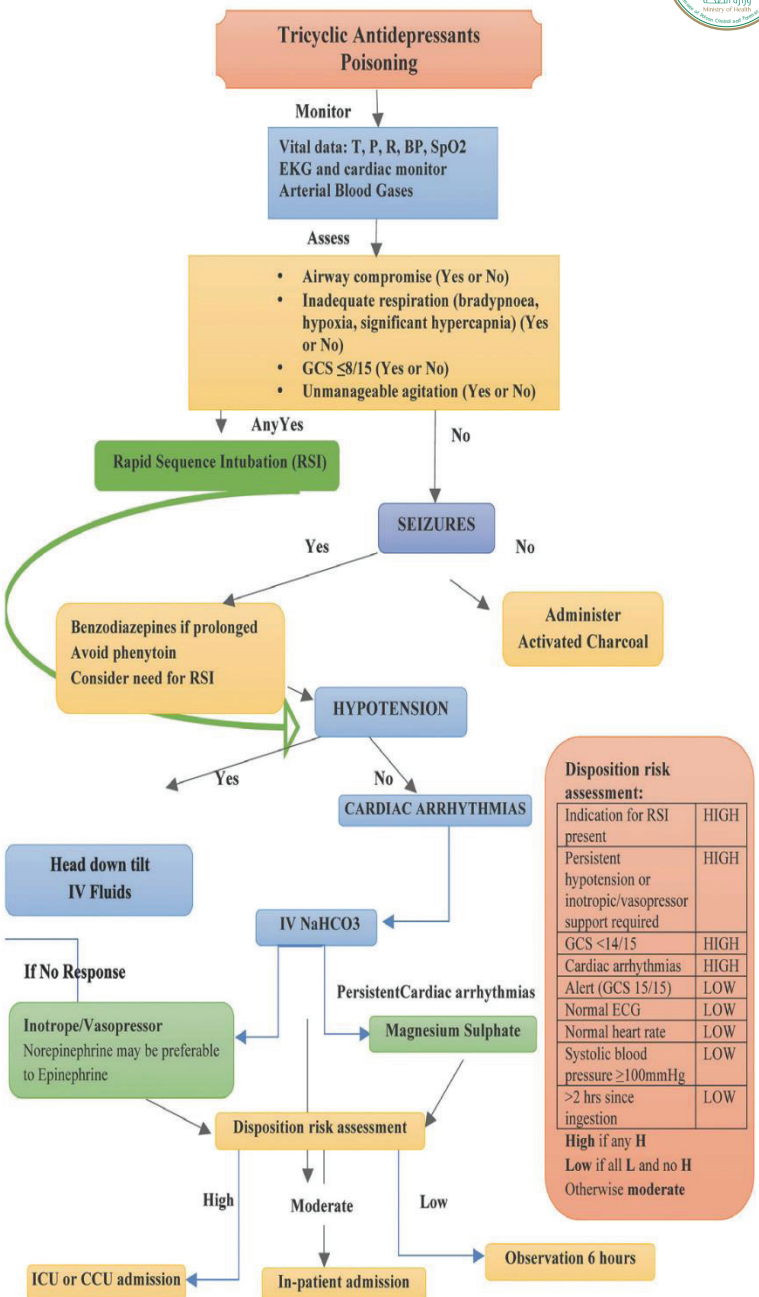
Treatment of hypotension or arrhythmia:

Sodium bicarbonate for cardiac toxicity (WIDE QRS COMPLEX)

- Sodium bicarbonate is the standard initial therapy for hypotension or arrhythmia due to TCA toxicity. It is indicated in patients with widening of the QRS interval > 100 msec or a ventricular arrhythmia.
- The initial dose of hypertonic sodium bicarbonate is 1-2 mEq/kg, given as a rapid IV push through a large bore IV catheter. In adults, one common approach is to give 2-3 vials or prefilled syringes (50 mL each) of 8.4 % sodium bicarbonate. If there is no response observed after the administration of the initial dose, it may be repeated after 5 minutes. It is advisable to run a continuous 12-lead EKG during the infusion to monitor for the presence (or absence) of narrowing of the QRS complex, a decrease in the R wave amplitude in lead AVR, or resolution of any arrhythmia.
- If the QRS narrows after bolus therapy, begin a continuous IV infusion of 150 mEq of sodium bicarbonate in 1 L of D5W and infuse at 250 mL/hour in adults.
- Frequent arterial blood pH measurements should be obtained during treatment with sodium bicarbonate; a reasonable goal pH is 7.50-7.55. Volume overload, hypokalemia, hypernatremia, and metabolic alkalosis may result from prolonged bicarbonate infusions, and clinical and laboratory parameters must be followed closely to avoid these complications.
- Measure the arterial pH hourly until it reachs the normal range and stable. After that, measurements may be obtained every 4-6 hrs. The serum potassium concentration should be measured concurrently with the arterial pH.

- Hypotension: Treat with intravenous boluses of isotonic crystalloid. If patient remains hypotensive despite aggressive volume resuscitation you can treat with a vasopressor. α-adrenergic agonists (e.g., neosynephrine, norepinephrine) are preferred.
- Infusion of lipid emulsion should be considered in patients with refractory hypotension or dysrhythmias.

  Seizures: Treat with benzodiazepines (e.g., diazepam 5 mg IV or lorazepam 2 mg IV) Do NOT treat with phenytoin
- Despite prominent anticholinergic toxicity in some patients with TCA poisoning, physostigmine is contraindicated as it is associated with cardiac arrest in the setting of TCA toxicity.


Tricyclic Antidepressants Poisoning
Monitor
Vital data: T, P, R, BP, SpO2
EKG and cardiac monitor
Arterial Blood Gases
Assess
Airway compromise (Yes or No)
Inadequate respiration (bradypnoea, hypoxia, significant hypercapnia) (Yes or No)
GCS ≤8/15 (Yes or No)
Unmanageable agitation (Yes or No)
AnyYes
No
Rapid Sequence Intubation (RSI)
SEIZURES
Yes
No
Benzodiazepines if prolonged
Avoid phenytoin
Consider need for RSI
Administer Activated Charcoal
HYPOTENSION
Yes
No
CARDIAC ARRHYTHMIAS
Head down tilt
IV Fluids
IV NaHCO3
If No Response
PersistentCardiac arrhythmias
Inotrope/Vasopressor
Norepinephrine may be preferable to Epinephrine
Magnesium Sulphate
Disposition risk assessment
High
Moderate
Low
ICU or CCU admission
In-patient admission
Observation 6 hours
Disposition risk assessment:
Indication for RSI present HIGH
Persistent hypotension or inotropic/vasopressor support required HIGH
GCS <14/15 HIGH
Cardiac arrhythmias HIGH
Alert (GCS 15/15) LOW
Normal ECG LOW
Normal heart rate LOW
Systolic blood pressure ≥100mmHg LOW
>2 hrs since ingestion LOW
High if any H
Low if all L and no H
Otherwise moderate

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ANTIPSYCHOTIC DRUGS

(INCLUDING PHENOTHIAZINES)

INTRODUCTION:

Description:

- Phenothiazines, butyrophenones, and other related medications are used widely to treat psychosis and agitated depression. In addition, some of these medicatics (eg, prochlorperazine, promethazine, and droperidol) are prescribed as antiemetic drugs.
- Suicidal overdoses are common, but because of the high toxic therapeutic ratio, acute overdose rarely develops in death.
- A large number of newer therapeutic agents that often are referred to as “atypical antipsychotics” have been developed. Atypical antipsychotics differ from other neuroleptic agents in their binding to dopamine receptors and their acts on dopamine-mediated behaviors.
- Overdose experience with these agents is limited.

Forms and uses:

- They are used as antiemetic agents, pain medications, antipsychotic agents, and anxiolytic agents; they are also prescribed in the treatment of allergic reactions and hiccups.

Toxic dose:

- Extrapyramidal reactions, anticholinergic side effects, and orthostatic hypotension are often seen with therapeutic antipsychotic doses.
- Tolerance to the sedating effects of the antipsychotics is reported, and patients on chronic therapy may tolerate much larger doses than do other cases.
- The toxic dose after acute ingestion is highly variable.
- Serious CNS depression and hypotension may occur after ingestion of 200–1000 mg of chlorpromazine in children or of 3–5 g in adults.
- Poisoning varies widely by phenothiazines toxic exposure, but ingestion of several grams has been associated with death.

Pathophysiology:

- A variety of pharmacologic mechanisms are responsible for toxicity, involving mainly the cardiovascular and central nervous systems.
- **Cardiovascular system toxic action.**
    - Anticholinergic effects may develop tachycardia.

- Alpha-adrenergic blockade may develop hypotension, especially orthostatic hypotension. With very large overdoses of some antipsychotic agents, quinidine-like membrane-depressant effects on the heart may develop.
- Many of antipsychotic agents can produce QT prolongation.

- **Central nervous system toxic action.**
  - **Neurological depression.** Centrally mediated sedation and anticholinergic effects lead to CNS depression.
  - **Constricted pupil.** Alpha-adrenergic blockade develops small pupils despite anticholinergic effects on other systems.
  - **Dystonic reactions.** Extrapyramidal dystonic reactions are relatively common with therapeutic doses and probably are caused by central dopamine receptor blockade.
  - **Seizures**. The seizure threshold may be lowered by unknown mechanisms.
  - Poikilothermia. Temperature regulatory control is disturbed.
- **Toxicokinetics.**
  - Antipsychotic medication have large volumes of distribution (Vd = 10-30 L/kg), and most have long elimination half-lives (eg, chlorpromazine half-life = 18-30 hours). Elimination is mainly by hepatic metabolism.

Epidemiology:

- Antipsychotic toxicity is common.
- Toxic manifestations following exposure are typically mild to moderate toxic degree.
- Death from antipsychotic overdose is rare, occurring in cases with delayed antipsychotic medication treatment or co-ingestions.

Causes:

- Antipsychotic toxicity is usually attributable to a suicidal attempt.
- Child toxicity is reported as accidental form of toxicity.

Risk factors:

- Pediatrics are more susceptible to the extrapyramidal side manifestations of prochlorperazine.

- In geriatric cases hepatic impairment may result in antipsychotic medication accumulation from therapeutic doses.

CLINICAL MANIFESTAIONS

- Antipsychotic toxicity is mainly manifested in the cardiovascular system and CNS. Anticholinergic intoxication may occur as a result of ingestion of benztropine (Cogentin) or other co-administered drugs.
  - **Mild antipsychotic intoxication** develops sedation, small pupils, and postural hypotension. Anticholinergic effects include dry mouth, loss of sweating, tachycardia, and urinary retention. Controversy, clozapine causes hypersalivation through an unknown aetiology.
  - **Severe antipsychotic intoxication** may cause coma, seizures, and respiratory arrest. The EKG usually shows prolongation of QT-interval and occasionally prolongation of QRS complex. Hypothermia or hyperthermia may occur. Clozapine can develop a prolonged confusional state and rarely cardiac toxicity.
  - **Extrapyramidal dystonic manifestations** of therapeutic antipsychotic doses include torticollis, jaw muscle spasm, oculogyric crisis, rigidity, bradykinesia, and pill-rolling tremor.
  - **Neuroleptic malignant syndrome.** Patients on chronic antipsychotic therapy may develop the neuroleptic malignant syndrome, which is characterized by rigidity, hyperthermia, sweating, lactic acidosis, and rhabdomyolysis.
  - **Agranulocytosis.** Clozapine therapy has been associated with agranulocytosis.
  - **Chemical sensitivity reaction.** Promethazine can produce severe tissue damage after perivascular extravasation, intraneural, or perineural injection. IV administration is not recommended unless the line is freely flowing and the promethazine drug is given very slowly.

INVESTIGATIONS

General Tests:

- **EKG and cardiac monitoring:**

  EKG effects are similar to type 1 antidysrhythmics effects such as quinidine like action (QRS or QT prolongation, ventricular dysrhythmia).

Sinus tachycardia is common and indicates sufficient antipsychotic drug absorption to produce anticholinergic effects.

- Other useful laboratory and general tests:
  electrolytes, glucose, BUN, creatinine, creatine kinase (CK), arterial blood gases or oximetry, abdominal radiography (radiopaque pills), and chest radiography.

Specific Tests:

- **Quantitative antipsychotic** blood levels are not routinely available and do not help in diagnosis or treatment.
- **Qualitative antipsychotic** screening may easily detect phenothiazines in urine or gastric juice, but butyrophenones such as haloperidol medication are usually not included in basic toxicologic screens

TREATMENT

Emergency and supportive measures

- Keep an open airway and assist ventilation if required.
- Administer supplemental 100% oxygen.
- Treat coma, seizures, hypotension, and hyperthermia if they develop.
- Close monitor vital signs and EKG for at least 6 hours and admit the cases for at least 24 hours if there are signs of significant toxicity.
- Pediatrics with antipsychotic toxicity should be evaluated for possible intentional abuse.

Specific drugs and antidotes.

- There is no specific antidote.
- **Dystonic reactions.**
  - Give diphenhydramine, 0.5-1 mg/kg IM or IV, or benztropine.
- **QRS-interval prolongation.**
  - Treat quinidine-like cardio toxic effects with Na bicarbonate, 1-2 mEq/kg IV.
- **Hypotension**.
  - Hypotension from these drugs probably involves vasodilation induced by alpha1 receptor blockade. Treat with IV fluids and, if needed, a vasoconstrictor such as norepinephrine or phenylephrine.
  - Theoretically, medications with beta-2 activity (eg, epinephrine, isoproterenol) may worsen hypotension.

- **QT prolongation.**
  - QT prolongation and torsade may respond to magnesium infusion or overdrive pacing.

Decontamination.

- Give activated charcoal orally if conditions are appropriate.
- Gastric lavage is not necessary after small to moderate ingestions if activated charcoal can be adminstrated promptly.

Enhanced elimination.

- Owing to extensive tissue distribution "large volume of distribution", these drugs are not effectively removed by dialysis or hemoperfusion.
- Repeat-dose activated charcoal has not been evaluated completely.

FOLLOW UP

Patient monitoring

- Close continuous respiratory and cardiac monitoring and serial EKGs should be instructed.
- Fluid and electrolytes levels, liver and renal function tests, and clinical indicators of toxicity should be followed.

Expected course and prognosis

- Most cases who overdose on phenothiazines recover within 24-48 hours.
- Death may develop in severe cases involving dysrhythmia, seizures, hypotension, or hyperthermia

Discharge criteria/instructions

- **From the emergency department.** Cases may be discharged if they did not develop seizure or QRS widening, hypotension, or dysrhythmia (other than mild transient sinus tachycardia) during 6 hours of close observation, and after they have received GIT decontamination and, if indicated, a psychiatric evaluation.
- **From the hospital.** Cases may be discharged from the hospital after all clinical manifestations have resolved (hypotension, QRS widening, CNS depression, and dysrhythmia) and after the EKG record has been return normal for 24 hours duration.

PITFALLS

Diagnosis

- Extended-release products may require admission and extended close observation.

Treatment

- Incomplete decontamination may result in prolonged manifestations or delayed deterioration course.

Follow-up

- Inadequate observation time may result in missing late antipsychotic complications of extrapyramidal manifestation or neuroleptic malignant syndrome.

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BENZODIAZEPINES

INTRODUCTION:

Description:

- The drug class of benzodiazepines includes many compounds that vary widely in potency, duration of action, presence or absence of active metabolites, and clinical usage.
- Three non-benzodiazepines compounds; eszopiclone, zaleplon, and zolpidem, have similar clinical effects and are included here.
- In general, death from benzodiazepine overdose is rare unless the medications are combined with other CNS-depressant preparations, such as ethanol, opioids, and barbiturates.
- Newer potent, short-acting benzodiazepines agents have been considered the sole cause of death in recent reported forensic cases.

Forms and uses:

- The benzodiazepines formulations are used as sedatives, anxiolytics, and muscle relaxants, and include alprazolam (Xanax), brotizolam, chlordiazepoxide (Librium), chlorazepate (Tranxene), clobazam, clonazepam (Clonopin), diazepam (Valium), estazolam (Prosom), flurazepam (Dalmane), halazepam, lorazepam (Ativan), lormetazepam, medazepam, midazolam (Versed), nitrazepam, oxazepam (Serax), prazepam, temazepam (Restoril), triazolam (Halcion).

Toxic dose:

- Generally, the toxic therapeutic ratio for benzodiazepines is very high. For example, oral overdoses of diazepam have been reported in excess of 15-20 times the therapeutic dose without serious depressive action of consciousness level.
- However, respiratory arrest has been reported after ingestion of 5 mg of triazolam and after rapid IV injection of diazepam, midazolam, and many other benzodiazepines.
- Also, ingestion of another medication with CNS-depressant properties (eg, ethanol, barbiturates, and opioids) probably will produce additive toxic CNS inhibitory effects.

Pathophysiology:

- Benzodiazepines augment the action of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). They also inhibit other neuronal systems by poorly detected mechanisms.
- Hyperpolarization due to transmembrane chloride ion flux through a GABA-mediated channel produces decreased neuronal excitability "High threshold Status". Benzodiazepines toxic effects are typically mild to moderate.
- The result is generalized depression of spinal reflexes and the reticular activating system. This can lead to coma and respiratory arrest.
    - **Benzodiazepines respiratory arrest.**
        - It is more likely with newer short-acting benzodiazepines agents such as triazolam, alprazolam, and midazolam.
        - It has also been reported with "Non-benzodiazepine agent" zolpidem.
    - **Benzodiazepines cardiopulmonary arrest.**
        - It has occurred after rapid injection of diazepam, possibly because of CNS-depressant effects or because of the toxic effects of the diluent propylene glycol.
- **Pharmacokinetics properties.** Most of these benzodiazepines medications are highly protein-bound (80-100%).

Epidemiology:

- Benzodiazepines intentional ingestion is common
- Death develops rarely, usually involving coingestant of neurological depressant agent such as ethanol, which augment respiratory depression
- Young children are at increased risk of accidental poisoning.
- The elderly cases are at risk, usually due to depressed renal and hepatic metabolic and excretory function.

Causes:

- Toxic ingestion is usually reported both intentional and unintentional cases.

Drug interactions:

- Toxic manifestations may be enhanced with co-ingestion of CNS depressants such as, ethanol, barbiturates, or other CNS depressants.

CLINICAL MANIFESTAIONS

- Onset benzodiazepines of CNS depression may be observed within 30-120 minutes of ingestion, depending on the type of compound.
- Lethargy, slurred speech, ataxia, “silent” coma, and respiratory arrest may develop.
- Generally, patients with benzodiazepine-induced coma have hyporeflexia and midposition or small pupils. Hypothermia may present.
- Serious complications are more likely when newer short-acting benzodiazepines agents are involved or when other depressant drugs have been coingested.

INVESTIGATIONS

General Tests:

- Other useful laboratory tests include glucose, arterial blood gases, and pulse oximetry.

Specific Tests:

- Benzodiazepines detection test:
  - Serum benzodiazepines drug levels are often available from commercial toxicology laboratories but are rarely of value in emergency management.
  - Urine and blood qualitative screening may direct rapid confirmation of exposure.
  - Immunoassays are sensitive to the benzodiazepines that metabolize to oxazepam (eg, diazepam, chlordiazepoxide, and temazepam), but may not detect newer benzodiazepines or those in low concentrations “pseudonegative results”.

TREATMENT

Emergency and supportive procedures:

- Protect the airway and assist ventilation if required.
- Treat coma, hypotension, and hypothermia if they develop “as general toxicology section”.
- Hypotension usually responds effectively to supine position and IV fluids.

Antidotes.

Flumazenil

- Flumazenil is a specific benzodiazepine receptor antagonist that can rapidly reverse benzodiazepine coma.

- However, because benzodiazepine toxicity by itself is rarely fatal, the role of flumazenil in routine treatment has not been established.
- It is administered IV with a starting dose of 0.1-0.2 mg, repeated as needed up to a maximum of 3 mg.
- It has some important potential drawbacks:
- It may develop seizures in patients who have co-ingested medications with proconvulsant activity effect.
- It may develop acute withdrawal, including seizures and autonomic instability, in cases who are benzodiazepines addicted.
- Resedation is common when the drug wears off after 1-2 hours "short ½ life", and repeated flumazenil dosing or a continuous infusion is often required.

Decontamination.

- Consider activated charcoal if the ingestion occurred within the previous 30 minutes and other conditions are appropriate.
- Gastric lavage is not necessary after small to moderate ingestions if activated charcoal can be given promptly.

Enhanced elimination.

- There is no benefit role for diuresis, dialysis, or hemoperfusion.
- Repeat-dose charcoal has not been completed studied.

FOLLOW UP

Patient monitoring

-Cases should have close continuous respiratory & hemodynamic monitoring.

Expected course and prognosis

- Cases usually regain consciousness within 24 hours.
- Most cases recover completely unless hypoxia develops

Discharge criteria/instructions

- **From the emergency department.** Asymptomatic cases may be discharged after decontamination procedures, a 6-hour close observation period, and psychiatric assessment, if required.
- **From the hospital.** Cases may be discharged when vital signs and mental condition become stable & after psychiatric assessment, if indicated.

PITFALLS

Diagnosis

- Manifestations of benzodiazepine toxicity may closely resemble other medical conditions (both other ingestions and non-toxicologic conditions “hypoxia, hypoglycemia, intracranial injury, meningitis, encephalitis, or postictal state), resulting in misdiagnosis.

Treatment

- Benzodiazepine Agents with long half-lives may require extended observation and care.

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SUBSTANCES OF ABUSE

AMPHETAMINES AND CATHINONES

INTRODUCTION:

- Methamphetamine is a sympathomimetic amine that first appeared as a nasal decongestant in the form of benzedrine inhaler. Furthermore, it is also used for the treatment of attention deficit hyperactivity disorder, obesity and as an off-label treatment for narcolepsy. Currently, there is a worldwide epidemic use of recreational methamphetamine and other amphetamine-derived stimulants such as methylenedioxymeth-amphetamine (MDMA) also known as ECSTASY. This is more commonly noticed among youth as it is 10 times more potent than amphetamine.
- Synthetic cathinones (bath salts) are analogues of a naturally occurring substance found in the leaves of Catha edulis (Khat), but characteristics similar to other amphetamines would be expected based upon their structural similarities.

TOXIC DOSE:

- The toxic dosage is variable; therefore, serial observation of the patient is used to evaluate the degree of severity.
- Repeated amphetamine users develop tolerance; therefore, higher doses are needed to develop toxicity.

PATHOPHYSIOLOGY:

- Amphetamines are indirectly acting sympathomimetic substances that stimulate norepinephrine release & have direct agonist actions on alpha- and beta-adrenergic receptors.

EPIDEMIOLOGY:

- Amphetamine poisoning is common, with wide regional variations in the incidence of abuse pattern.
- Toxic manifestations following exposure are typically mild to moderate degree.
- Death develops in cases abusing amphetamines at escalating doses.

CAUSES:

- Poisoning often develops from recreational abuse.
- Child neglect or abuse should be considered if the patient is less than one year of age, suicide attempt if the patient is over six years of age.

MECHANISM OF TOXICITY:

- Methamphetamine produces its stimulant effects indirectly through being incorporated into cytoplasmic vesicles where it displaces epinephrine, norepinephrine, dopamine, and serotonin into the cytosol. As cytosolic concentrations rise, neurotransmitters diffuse out of the neuron and into the synapse where they activate postsynaptic receptors. Meth-amphetamine also inactivates neurotransmitter reuptake transporter systems. These two processes result in adrenergic receptor activation. The lone modulatory response to such stimulation is degradation by catechol-O-methyl transferase (COMT), a slow, saturable degradation pathway.
- On the other hand, the full mechanism of action of cathinones is not fully understood but some cathinone analogues such as methylone and pyrovalerone are hypothesized to inhibit reuptake of norepinephrine and dopamine with serotonin like effects.

CLINICAL FEATURES:

- CNS: Amphetamine and/or cathinones generally cause feelings of euphoria, empathy, excitement, and wellbeing as well as CNS hyperstimulation and agitation.
- Cardiac: Hypertension, tachycardia, hyperthermia, mydriasis and diaphoresis, combativeness, hallucinations, paranoia, confusion, myoclonus, and in rare cases seizures.
- Musculoskeletal: Persistent myoclonus and tremors.
- Skin: Injection of amphetamines has been associated with extensive cellulitis, abscess formation, and necrotizing fasciitis leading to amputation.
- Renal: Acute renal injury with evidence of acute tubular necrosis has been reported after abuse of synthetic cathinones.
- Miscellaneous: Less commonly, seizures, stroke, myocardial infarction and hypertensive crisis may be the leading presentation of amphetamine and/or cathinone toxicity.
- Electrolytes: Hypokalemia, hyponatremia, hypermagnesemia, and elevated anion gap acidosis are common findings following amphetamine intoxication.

DISTINGUISHING AMPHETAMINE TOXICITY FROM CATHINONE TOXICITY

- The most distinguishing feature of overdose with a synthetic cathinone compared to amphetamine is the prolonged duration of effect observed with cathinones. Many reports of "bath salt" cases describe agitated delirium and psychotic features lasting for days to even weeks. These compounds should be considered a possible cause in any case with such prolonged symptoms.

DIFFERENTIAL DIAGNOSIS:

- Toxicologic: Anticholinergics, hallucinogens, withdrawal from benzodiazepines and cocaine overdose.
- Non toxicologic: Thyrotoxicosis, pheochromocytoma, heat stroke and paranoid schizophrenia.

INVESTIGATIONS:

Routine:

- Bed Side RBS to exclude hypoglycemia.
- ABGs and Electrolytes.
- BUN, Creatinine, ALT, AST, Creatine Kinase.
- Serum Paracetamol, Salicylates.
- EKG.
- Pregnancy test for females in child bearing period.

Specific:

- Urine screening for amphetamines and cathinones as well as, other drugs of abuse (Benzodiazepines, Barbiturates, Cannabis and Alcohol) to identify polydrug use.
- Amphetamine can be qualitatively tested in urine using immunoassay technique. Positive results indicate recent amphetamine intake (2-3 days).
- CT brain to exclude cerebral hemorrhage.

TREATMENT:

Stabilization:

- The mainstay of management is to secure airway, breathing, and circulation and control sympathetic overstimulation and agitation.
- Standard rapid sequence medications are to be used. Manage severe hypertension initially with benzodiazepines (e.g., Lorazepam, 1-2 mg IV, may repeat as necessary. In the case of absence of IV access, midazolam 3-5 mg IM, may repeat as needed).

- If hypertension is refractory, administer nitroprusside infusion 0.25-10 µg/kg/min IV infusion or phentolamine 5-15 mg IV bolus every 5-15 min.
- Chest pain: Administer oxygen, aspirin and nitroglycerin if chest pain does not respond to benzodiazepines. DO NOT administer β-blocking agents.

Decontamination:

- Administer one dose of activated charcoal (1 gm/kg, maximum dose 50 gm) for ingestions occurring within less than 1 hour if airway is protected.

Symptomatic:

- Agitation and/or seizures: Administer benzodiazepines (e.g., Lorazepam 1-2 mg IV or midazolam 3-5 mg IM). These medications may be repeated as needed.
- Hyperthermia: Active external cooling and benzodiazepines.
- Hyponatremia: If hyponatremia is mild or moderate (above 115 mEq/dL), restrict fluids.
- If Hyponatremia causes persistent seizures: Administer benzodiazepines (e.g. lorazepam 1-2 mg IV or midazolam 3-5 mg IM). May be repeated as needed. Additionally, if serum sodium = or < 115 mEq/dL, administer hypertonic saline (3% or 513 mEq/L) 100 mL as IV bolus. If seizures persist, administer one or two additional doses of 100 mL over 10 minutes each.
- The treatment of children with amphetamine intoxication is similar to that of adults, but special consideration should be directed towards aggressive cooling measures and close monitoring of vital signs and urine output. Hydration should be sufficient to maintain urine output.

COMMON PITFALLS:

- In case of agitation, DO NOT give butyrophenones (e.g., haloperidol) and DO NOT give Phenytoin
- In patients presenting with hyperthermia DO NOT give antipyretics.
- In case of hyponatremia presenting with seizures; monitor serum sodium closely; DO NOT give phenytoin.

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COCAINE OVERDOSE

INTRODUCTION:

- Cocaine is a natural stimulant (sympathomimetic) that increases energy and produces euphoria. Cocaine is extracted from the leaves of the coca plant (Erythroxylum coca), which is indigenous to the Andean highlands of South America. Cocaine produces toxicity in virtually every organ system, principally via hemodynamic effects.

MECHANISM OF TOXICITY:

Cocaine produces its stimulant effects through 3 main pathways:

- Blockade of the reuptake of biogenic amines especially norad-renaline at the adrenergic receptors through blockade of reuptake.
- Elevation of the levels of the excitatory amino acids glutamate and aspartate in the brain, particularly in the nucleus accumbens.
- Blocking slows or blocks nerve conduction and act as a local anaesthetic by altering the recovery of the neuronal Na^+ channels.

CLINICAL FEATURES:

Cocaine overdose may present with clinical features very similar to amphetamine overdose, and the main presentation could be, stroke, angina or myocardial infarction.

- Cardiac: Chest pain, hypertension, tachycardia and shortness of breath.
- Lungs: Decreased Breath sounds after smoking crack can lead to pneumothorax.
- Neurological: Agitation, headache, focal neurological symptoms, and extremity symptoms are particularly worrisome.
- Hyperthermia may occur.
- Pupils: Mydriasis.
- Extremities: reduced pulse volume could suggest vascular pathology e.g., Aortic Dissection.
- GIT: Ischemic colitis, mesenteric vascular occlusion.
- Kidney: Renal infarction, renal failure as a result of rhabdomyolysis.

DIFFERENTIAL DIAGNOSIS:

- Toxicological: Anticholinergics, hallucinogens, amphetamine, cathinone and withdrawal from benzodiazepines.
- Non toxicological: Thyrotoxicosis, pheochromocytoma, heat stroke, and paranoid schizophrenia.

INVESTIGATIONS:

Routine:

- Bed Side RBS to exclude hypoglycemia
- ABGs, BUN, Creatinine, ALT, AST, Creatine Kinase.
- Serum Paracetamol, Salicylates.
- EKG and Pregnancy test for females in child bearing period.

Specific:

- Urine toxicology screen for cocaine metabolite (Benzoylecgonine) as cocaine is rapidly eliminated. Benzoylecgonine can still be detected in urine for up to 3 days using immunoassay and Gas Chromatography Mass Spectometry (GCMS). Screen for other drugs of abuse for confirmation of intake.
- Driven by clinical symptoms (e.g. Cardiac enzymes for suspected MI and CT for suspected aortic dissection.
- CT brain to exclude cerebral hemorrhage

TREATMENT:

Stabilization:

- Airway: Succinylcholine is relatively contraindicated in rapid sequence intubation; consider rocuroniu (1 mg/kg IV) or other non-depolarizing agents as an alternative.

Symptomatic:

- Psychomotor agitation: Administer benzodiazepines (e.g., diazepam 5-10 mg IV q 3-5 minutes until agitation controlled)
- Severe symptomatic hypertension:
  - Administer diazepam (5 mg IV) or lorazepam (1 mg IV); may repeat q 5 minutes until sedated.
  - Aspirin 325 mg PO (Contraindicated if aortic dissection is suspected)
  - Nitroglycerin 0.4 mg SL.
  - Phentolamine 1-5 mg IV, repeats as necessary and hold if systolic blood pressure < 140 mmHg.
  - In case of QRS widening, administer 1-2 meq/kg of $NaHCO_3$.

COMMON PITFALLS

- The administration of β-Blockers is contraindicated in controlling cocaine-induced hypertension.
- Administration of phenothiazines and butyrophenones is contraindicated as they decrease seizure threshold

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OPIATES

INTRODUCTION:

- Opiates are part of a larger class of drugs, the opioids. Opioid abuse is a worldwide problem and mortality from opioid overdose is common and increasing.

EPIDEMIOLOGY:

- Opiates intoxication is common
- Toxic manifestations following narcotic exposure are typically moderate, with death occurring from central respiratory depression.

CAUSES:

- Manner of use is typically intentional in adults, accidental in pediatrics.
- Child neglect or abuse should be considered if the patient is less than one year of age, suicide attempt if the patient is over six years of age.

RISK FACTORS:

- Persistent severe intolerable pain (e.g., severe toothache or headache) may predispose to overuse.

DRUG AND DISEASE INTERACTIONS:

- Narcotics potentiate CNS depressive effect of sedative-hypnotic medications and other respiratory depressants drugs.
- Meperidine and monoamine oxidase inhibitors formulation may develop serotonin syndrome.
- Methadone serum levels are declined by chronic use of carbamazepine, phenytoin, and rifampin, developing withdrawal.

MECHANISM OF TOXICITY:

- Opiates produce their effects through activation of mu opioid receptor subtype. Theses receptors are G-protein coupled receptors and are responsible for mediating reward, withdrawal and analgesia. Mu receptors are located centrally and peripherally. Activation of the central mu receptors is responsible for mediating responses such as euphoria, respiratory depression, analgesia and miosis. Activation of peripheral mu receptors produces constipation and cough suppression.

CLINICAL MANIFESTATIONS:

- Changes in mental status ranging from mild euphoria or lethargy to coma.
- Miotic (Pinpoint) pupils.
- Decreased bowel sounds.
- Decreased to normal heart rate and blood pressure.

- Hypoventilation (The best predictor of opioid poisoning).
- Important: Patients presenting with normal pupils does not exclude Opioid Intoxication. Drugs like Meperidine and Propoxyphene may present with normal pupils. Other co-ingestants such as sympathomimetics or anticholinergics may present with normal pupils.

TOXICITIES OF SPECIFIC AGENTS:

- In addition to the general features described above, some agents have specific toxicities. A brief description of the notable, yet infrequent, effects and characteristics of several opioids commonly encountered in the overdose patient follow:
  - Buprenorphine – Partial opioid agonist, may induce withdrawal in opioid-dependent patients.
  - Dextromethorphan – Serotonin syndrome, at high doses exhibits some μ effects of opioids (miosis, respiratory and CNS depression), but is not a pure opioid agonist.
  - Fentanyl – Very short acting.
  - Hydrocodone – Often combined with acetaminophen.
  - Meperidine – Seizure, serotonin syndrome (in combination with other agents).
  - Methadone – Very long-acting; QTc prolongation, Torsades de Pointes.
  - Oxycodone – Often combined with acetaminophen; possible QTc interval prolongation.
  - Propoxyphene – QRS prolongation and seizures
  - Tramadol – Seizures.

INVESTIGATIONS:

Routine:

- Bed Side RBS to exclude hypoglycemia.
- ABGs, Electrolytes.
- BUN, Creatinine, ALT, AST, Creatine Kinase.
- Serum Paracetamol, Salicylates.
- EKG.
- Pregnancy test for females in child bearing period.

Specific:

- Urine screening for opiates as well as other drugs of abuse (Benzodiazepines, Barbiturates, Cannabis and Alcohol) to identify polydrug use.

DIFFERENTIAL DIAGNOSIS:

Toxic agent	Defining Features
Antihistamines	Anticholinergic toxidrome
Antipsychotics	Pupils not constricted, bowel sounds normal
Barbiturates	Mild to severe hypotension, serum concentration
β-adrenergic antagonists	Cardiovascular findings (hypotension, bradycardia) more prominent than mental status findings
CalciumChannel blockers	Cardiovascular findings (hypotension, bradycardia, or tachycardia) more prominent than mental status findins
Carbamazeine	Serum concentration
Carbon monoxide	Carboxyhemoglobin level
Clonidine	Bradycardia and hypotension
Cyclic antidepressants	QRS prolongation, hypotension, tachycardia
Ethanol	Pupils and bowel sounds normal, serum concentration
Ethylene glycol	Pupils and bowel sounds are normal
Hypoglycemic agents	Serum glucose concentration
Isoniazid	History of seizures, normal pupils and bowel sounds
Isopropanol	Pupils and bowel sounds normal
Lithium	Tremor, hyper-reflexia, serum concentration
Methanol	Pupils and bowel sounds normal
Organic-phosphorous compounds	Cholinergic toxidrome
Phencyclidine	Nystagmus (horizontal, vertical, or rotary)
Sedative-hypnotic agents	Pupil size normal to decreased, bowel sounds normal and less respiratory depression

TREATMENT:

Stabilization:

The main aim of Naloxone administration is the reversal of respiratory depression and not full regaining of consciousness or precipitating withdrawal.

- Reversal of respiratory depression with therapeutic opioid use and after postoperative overdose: If the O2 saturation is <94 % on room air but the patient is breathing spontaneously, administer 100% supplemental oxygen followed by IV naloxone 0.04 to 0.4 mg; given

or IM. Methodology: Dilute 0.4 mg/mL (1 mL) into 9 mL of 0.9% saline to reach a total volume of 10 mL to achieve a 0.04 mg/mL (40 µg/mL) concentration.

- If the patient is apneic, ventilate using a bag-valve mask attached to 100% supplemental oxygen and administer naloxone in doses of 0.2-2 mg IV or IM. If no response occurs after a total of 5-10 mg of naloxone, reconsider the diagnosis and perform tracheal intubation.
- In case of absence of IV access, Naloxone can be administered IM. Repeat until ventilation becomes adequate. If the desired response is not observed after a total dose of 0.8 mg, consider other causes of respiratory depression. Naloxone may be given endotracheal (off-label route) as 2-2.5 times the initial IV dose.
- Continuous IV infusion: For use with exposures to long-acting opioids (e.g. methadone) or sustained-release products or if hypoventilation recurs following the initial naloxone bolus.
- Administer additional bolus doses aiming to restore adequate ventilation. When ventilation is adequate, a naloxone infusion can replace frequent rebolusing. Begin the infusion rate at 2/3 of the total dose of naloxone needed to restore breathing, delivered every hour. Adjust the infusion rate as needed to assure adequate ventilation and prevent withdrawal symptoms.
- Opioid-dependent patients that are under treatment for cancer pain: Administer naloxone IV 0.04-0.08 mg (40-80 µg) slow IV push every 30-60 seconds until improvement of symptoms. If the patient does not show any response after a total naloxone dose of 1 mg, consider other causes of respiratory depression.
- If the respiratory rate is ≥ 12 breaths/minute and O_2 saturation is >94 % on room air, observe the patient in a monitored setting and frequently reassess. End-tidal CO2 monitoring using capnography is an excellent means to monitor ventilation.
- If the patient develops signs of opioid withdrawal, stop the infusion. If respiratory depression returns, start the infusion at half the original rate.
- The patient is medically stable for transfer or discharge when the mental status and ventilation remain normal for more than one hour after cessation of naloxone.

FOLLOW UP:

PATIENT MONITORING

- Respiratory and cardiac status must be monitored continuously.
- Possible sequelae involve renal impairment and neurological damage secondary to prolonged seizure and myocardial or CNS damage from hypoxic effects.

EXPECTED COURSE AND PROGNOSIS

- The prognosis is detected by the hypoxic damage that developed before management or the muscle damage from lying on an extremity for a prolonged duration.

DISCHARGE CRITERIA/INSTRUCTIONS

- From the emergency department. For most narcotics, asymptomatic cases may be discharged following decontamination procedure, a six hour observation period, and psychiatric assessment, if required.
- From the hospital. Cases may be discharged after mental condition, EKG, and vital signs records return to normal values, and decontamination procedures and psychiatric assessment are completed, if required.

PITFALLS:

DIAGNOSIS

- Pinpoint pupils sign may be obscured by hypoxic effect or components that develop mydriasis, such as scopolamine.
- Several medical formulations containing narcotics also contain acetaminophen or aspirin

FOLLOW-UP

- Discharge of the patient immediately after naloxone therapy may allow the recurrence of respiratory depression status outside of the emergency department.

Frequently encountered opioids and their equivalence to 10 mg Morphine

Source	Serum Half-Life (Hours)*	Approximate Equivalence To 10 Mg Morphine Injection (Mg)	Important Clinical Features
IMPORTANT: The Doses Included Here Are NOT Recommended For The Initiation Of Therapy; They Provide Equivalents For The Purpose Of Comparing Different Opioids.			
Natural			
Morphine	1.9 +/– 0.5	10 SC/IM/IV - 30 PO	
Codeine	2.9 +/– 0.7	75 SC/IM/IV 130 to 200 PO	Metabolized by CYP2D6 to active drug (morphine). Metabolism and effects are subject to pronounced individual variability. Single oral doses over 65 mg tend to produce disproportionately greater adverse effects than analgesia.
Semi-synthetic			
Hydromorphone	2.4 +/– 0.6	1.5 SC/IM/IV 7.5 PO	Hepatically metabolized to metabolites that can accumulate in organ failure and prolong effects. Some metabolites have been linked to neurotoxicity.
Oxycodone	2.6 (2.1-3.1)	20 to 30 PO	Metabolized by CYP3A4 and 2D6. Prolonged effects and elevated serum concentrations with renal or hepatic insufficiency. May cause QTc prolongation.
Hydrocodone	4.24 +/– 0.99	30 PO	
Diacetylmorphine (diamorphine, heroin)		5 SC	Highly lipophilic causing more rapid CNS effects than morphine. Largely metabolized to morphine. Due to abuse potential is not available for clinical use in many countries.
Synthetic			
Meperidine	3.2 +/– 0.8	75 to 100 SC/IM 300 PO	Excitatory neurotoxicity may occur when normeperidine, a renaly-eliminated metabolite, accumulates.
Methadone	27 +/– 12	10 SC/IM/IV Highly variable. See clinical features.	Used in opioid substitution therapy. Can cause QTc prolongation. May be far more potent than indicated in this table. Half-Life (up to 150 hours), methadone has the highest risk among opioids of accumulation and toxicity during initial titration and after changes in dose.
Propoxyphene (dextropropoxyphene)		65 to 130 PO•	Usual initial dose for mild analgesia shown; NOT equivalent to parenteral morphine 10 mg. Has class IA anti-dysrhythmic properties, leading to widened QRS, negative inotropy, and conduction abnormalities. Can cause seizures. Onset of toxic effects is 15 to 60 minutes in overdose.

Source	Serum Half-Life (Hours)*	Approximate Equivalence To 10 Mg Morphine Injection (Mg)	Important Clinical Features
Tramadol	5.5 (4.5-7.5)	50 to 100 PO•	Usual initial dose for mild analgesia shown; NOT equivalent to parenteral morphine 10 mg. Effects NOT completely reversed by naloxone. Noted to cause seizures. Subject to interactions including serotonin excess.
Fentanyl	3.7 +/– 0.4	0.05 to 0.1 SC/IM/IV	Short acting when administered IV/IM as a single dose. Highly lipophilic. Parent drug accumulates with repeated or prolonged administration.
Agonist/antagonist			
Pentazocine	2 to 3	30 to 60 SC/IM - 75 to 150 PO	
Partial agonist			
Buprenorphine	2.33 +/– 0.24	0.3 to 0.4 IM/IV 0.4 sublingual	Used in opioid substitution therapy. Significantly longer duration of effect than 10 mg parenteral morphine. Metabolized by and subject to interactions involving CYP3A4.
Gastrointestinally insoluble – not analgesic			
Diphenoxylate		2.5 to 5 PO (anti-diarrheal dose)•	Poor solubility limits potential for parenteral injection and abuse. Usually formulated with atropine (US trade name Lomotil®, 0.025 mg atropine and 2.5 mg diphenoxylate) to further decrease abuse potential.
Loperamide		2 to 4 PO (anti-diarrheal dose)•	Very low abuse potential due to lack of effect on CNS receptors.

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CANNABIS

INTRODUCTION:

DESCRIPTION

- Cannabis is the popular name for the dried flowering leaves of Cannabis sativa, C. indica, and C. ruderalis, the active ingredient of which is delta-9-tetrahydrocannabinol (THC).

FORMS AND USES

- Other names for illicit cannabis are pot, weed, grass, ganja, hashish, bhang, charas, dagga, kif, reefer, marilyn, honey oil, fimble, and gallow grass; Cannabis is sometimes named according to its site of origin and color (e.g., Panama red or Acapulco gold).
- Sensemilla cannabis indicates to the flowering tops of the female plant, which contain the highest resin concentration.
- Hashish has a high content of THC and is obtained by extracting cannabis with a nonpolar solvent solution.
- Cannabis products may be added to food (e.g., cookies or brownies) (Prohibited in Saudi Arabia) or dissolved for intravenous abuse.
- Pharmaceutical formulation of cannabis involve dronabinol (Marinol) and nabilone (Cesamet).
    - Cannabis cigarettes and synthetic cannabinoids may be utlized as antiemetics medication usage for chemotherapy-induced nausea.
    - Other suggested medical indications for using THC include pain, seizures, asthmatic manifestations, glaucoma, and ulcerative colitis
    - Typical adult doosage are dronabinol, 2.5 mg orally twice a day, and nabilone, 1-2 mg orally twice a day.

TOXIC DOSE

- Acute oral intoxication is very low.
- The calculated human cannabis toxic dose after ingestion exposure is 30 mg/kg of cannabis; 15 mg/m^2 of THC has lead to central nervous system toxic manifestations in cancer patients.

PATHOPHYSIOLOGY

- Cannabis has at least 60 cannabinoid molecular structure, involving the most active ingredient, THC.
- The concentration of THC in cannabis cigarettes varies from 1% - 8%; hashish may contain 5% to 10% and hash oil up to 50% concentration.
- After smoking cannabis, approximately 20-50% of the THC is systemically absorbed, the onset of cannabis effects is 6-12 minutes, and manifestations may persist up to 3 hours

- After oral exposure, only 5% - 20% of THC is bioavailable due to first-pass hepatic metabolism effect. The onset of symptoms is delayed, 30-60 minutes and persists for 4-6 hours
- Comparing cannabis and tobacco smokers, cannabis usage was associated with a five time increase in carboxyhemoglobin concentrations and a three time increase in inhaled amount of tar.
- Carcinogenesis. Cannabis is implicated in high risk for mouth, head, neck, and bronchial cancer.

EPIDEMIOLOGY:

- Cannabis toxicity is common.
- Toxic cannabis effects following all routes of exposure are typically mild degree.
- Death from cannabis intoxication is rare and is usually resulted from associated traumatic injuries arising from impaired judgment.

CAUSES:

- Cannabis exposure is nearly always intentional exposure.
- Child neglect or abuse should be considered in pediatric cannabis intoxication
- Significant toxicity can be seen with accidental pediatric cannabis exposure by ingestion or inhalation.

DRUG INTERACTIONS

- Cannabis may act synergistically with other central nervous system depressing substances.
- Cannabis may potentiate cocaine-induced tachycardia and accelerate a subjective high.

CLINICAL MANIFESTAIONS

SIGNS AND SYMPTOMS

- Oral or inhalational cannabis abuse leads primarily desirable neurological effects (a "high").
- Intravenous infusion of dissolved cannabis extract can cause severe multiorgan toxicity and damage, involving severe gastroenteritis, fulminant hepatitis, acute renal impairment, anemia, severe thrombocytopenia, and leukocytosis.

Vital Signs

- Both hypothermia or hyperthermia, tachycardia or bradycardia, hypotension or hypertension, and bradypnea have been reported.

HEENT

- Conjunctival congestion, dropped intraocular tension, dilated pupil, horizontal nystagmus, blurred vision, uvula edema, and dryness of the mouth can develop.

Pulmonary

- Bradypnea, respiratory irritation, persistent coughing, and bronchodilation may develop.

Cardiovascular

- Both hypertension or hypotension, tachycardia or bradycardia, and a chest tightness sensation may develop.

Gastrointestinal

- Increased appetite, decreased gut movement, and constipating effect may develop.

Renal

- Urine retention may develop.

Musculoskeletal

- Skeletal muscle weakness and abnormal jerking movement may develop.

Neurologic

- Anti-motivational syndrome may develop in chronic cannabis cases.
- Seizures may develop in cases with a history of previous history of seizure disorder.
- Mild cannabis toxicity produces euphoria, a degree of somnolence, heightened awareness, generalized relaxation, alteration in time perception, and increased appetite also may develop.
- Moderate cannabis toxicity leads to short-term memory impairment, poor concentration power and poor attention, inability to act multi-step orders, alternating mood disorders involving laughing episodes and depression mode episodes, changed thought patterns, and disorientation status may develop.
- Extreme cannabis toxicity includes decreased power of strength and coordination capacity, generalized lethargy, ataxia, characteristic slurred speech, anxiety disorders and impending “fear” of death, muscle jerking disorder, central respiratory depression, and finally coma have been detected.

Reproductive

- Decreased sperm production and motility, increased abnormal sperm count, and decreased ovulation pattern may develop.

Endocrine

- Gynecomastia, as well as depressed levels of testosterone hormone, luteinizing hormone, growth hormone, and follicle-stimulating hormone may be detected.

INESTIGATIONS

General Tests

- Serum electrolytes, BUN, creatinine, and glucose may be indicated to evaluate other causes of seizures or disturbed conscious level.
- Liver functions tests, coagulation profile studies, and serum creatine kinase level may be increased in patients with fever or agitation status.
- EKG, serum paracetamol, and aspirin levels should be detected in an overdose condition to detect occult ingestion.
- Head CT, lumbar puncture, and toxicology studies should be ordered as required to detect other causes of seizure and disturbed conscious level.
- Urine substance of abuse for cannabis may remain positive for several weeks after acute clinical manifestations have recovered.

Specific Tests

- No specific tests are ordered in minimally symptomatic cannabis cases.

TREATMENT

- Treatment should focus on airway management and supportive care.
- For paranoia or panic attacks, the patient should be placed in a quiet room and treated with reassurance in a nonthreatening manner.
- The dose and time of exposure should be determined for all substances involved.

DIRECTING PATIENT COURSE

Health-care professionals should call a poison control center when:

- Severe cannabis manifestations are reported.
- The acute toxic manifestations are not consistent with acute cannabis toxic manifestations.
- Co-ingestants, drug interaction, or underlying pathological condition presents an unusual problem.

Patients should be referred to a health-care professional when:

- Attempted suicide or homicide is possible present.
- Patients or caregivers appear unreliable.
- Severe cannabis effects are reported.
- The poisoning effects are not consistent with cannabis toxicity.

Admission Considerations

- Inpatient acute cannabis treatment is indicated for patient persistently abnormal reported vital signs, disturbed consciousness level, or clinically significant damaged organ intoxications.

DECONTAMINATION

In Hospital

- Gastric lavage is recommended if the patient presents within 1 hour of a large ingestion or if serious effects are reported.
- A single dose of activated charcoal (1-2 g/kg) should be given if the patient has ingested a substantial amount of cannabis within the previous few hours from the time of hospital adminstration.

ANTIDOTES

- There are no specific antidotes for cannabis intoxication.

SUPPORTIVE TREATMENT

- To control agitation, the physician should give a benzodiazepine with which he has experience.
    - For diazepam medication, the adult dosage is 5-10 mg intravenously; the pediatric dose is 0.2-0.5 mg/kg intravenously, and doses are repeated at 10-minutes intervals, titrating to desired effect.
    - For lorazepam medication, the adult dosage is 1 to 2 mg intravenously; the pediatric dosage is 0.05-0.1 mg/kg intravenously. Doses are repeated at 10-minutes intervals, titrating to desired effect.
- The patient's respiratory function should be closely monitored for any cannabis toxic manifestations.

FOLLOW UP

PATIENT MONITORING

- If severe cannabis manifestations or complications occurred, electrolytes, renal function, and other laboratory tests indicated by the patient's clinical condition must be monitored.

EXPECTED COURSE AND PROGNOSIS

- Cannabis effects peak rapidly and persist for several hours, followed by complete resolution unless complications appear.
- Inhalation of cannabis has been associated with chest complication in the form of pneumothorax and pneumomediastinum

DISCHARGE CRITERIA/INSTRUCTIONS

- From the emergency department or hospital, discharge is indicated for alert fully consciousness patients with normal reported vital signs, easy good ambulation, and a reliable noticed caregiver, following psychiatric assessment, if needed.

PITFALLS

DIAGNOSIS

- It is important to detect other serious or treatable causes of disturbed consciousness level.

FOLLOW-UP

- Diagnosed cannabis patients should be referred for substance abuse treatment program.

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ETHANOL:

INTRODUCTION:

Description:

- Ethanol is frequently ingested recreationally *"Prohibited in Saudi Arabia"*.

Forms and uses:

- Commercial beer, wine, and liquors contain various concentrations of ethanol. Ethanol also is present in a variety of colognes, perfumes, aftershaves, and mouthwashes; some rubbing alcohols; many food flavorings (eg, vanilla, almond, and lemon extracts); pharmaceutical preparations (eg, elixirs); hand sanitizers; and many other products.
- Ethanol may also serve as a competitive medication in the emergency management of methanol and ethylene glycol toxicity.

Toxic dose:

- Generally, 0.7 g/kg of pure ethanol (approximately 3-4 drinks) will develop a blood ethanol level of 100 mg/dL.
- The legal limit for ethanol in Saudi Arabia 30 mg/dL.
- A level of ethanol of 100 mg/dL depresses reaction time and judgment and may be enough to inhibit gluconeogenesis and produce hypoglycemia in children and patients with liver impairment, but by itself it is not enough to develop coma**.**
- The ethanol level sufficient to develop deep coma or respiratory depression is widely variable, depending on the individual's degree of tolerance to ethanol. Although concentrations above 300 mg/dL usually cause alcoholic coma in recently onset drinkers, patients with chronic alcoholism may be awake with alcoholic concentrations of 500-600 mg/dL or more.

Pathophysiology:

- **CNS depressant action:**
  - Central nervous system (CNS) depression is the primary effect of acute ethanol toxicity. Ethanol has additive effects with other CNS depressants medications, such as barbiturates, benzodiazepines, opioids, antidepressants, and antipsychotics.
- **Hypoglycaemic action:**
  - Hypoglycemia may be caused by impaired gluconeogenesis in

alcoholic cases with depleted or low glycogen stores (particularly pediatric and malnutironed cases).

- **Predisposing action for multiple pathological conditions:**
  - Ethanol toxicity and chronic alcoholism also predispose cases to trauma, exposure-induced hypothermia, GI tract damage and nervous system, and a number of nutritional disorders and metabolic disturbances.
- **Pharmacokinetics.**
  - Ethanol is readily completely absorbed from all GIT mucosa (peak, 30-120 minutes) and distributed into the body water (volume of distribution, 0.5-0.7 L/kg).
  - Ethanol elimination is mainly by oxidation in the liver and follows zero-order kinetics. The average adult case can metabolize about 7-10 g of ethanol per hour, or about 12-25 mg/dL/h. This rate varies among cases and is influenced by polymorphisms of the alcohol dehydrogenase enzyme "hyper or hypo metabolizer" and the activity of the microsomal ethanol-oxidizing enzymes systems.

Epidemiology:

- Accidental ethanol toxicity is common.

CLINICAL MANIFESTAIONS

Acute intoxication

Mild to moderate toxicity:

With mild to moderate ethanol toxicity, cases exhibit euphoria, mild incoordination, ataxia, nystagmus, and impaired judgment and reflexes. Social and moral ethics are loosened, and aggressive behavior is commonly reported. Hypoglycemia may develop, especially in pediatrics and persons with depleted hepatic glycogen stores.

Severe toxicity:

With deep ethanol toxicity, coma, respiratory depression, and pulmonary aspiration may develop. In these cases, the pupils are usually constricted, and the temperature, blood pressure, and pulse rate are often depressed. Rhabdomyolysis may develop from prolonged immobility.

Chronic intoxication

Chronic ethanol abuse is associated with several complications:

- Hepatic alcoholic intoxications involves fatty infiltration of the liver, alcoholic hepatitis, and cirrhosis. Hepatic scarring leads to portal hypertension, ascites, and bleeding manifestations from esophageal varices and hemorrhoids; hyponatremia from fluid retention; and bacterial peritonitis.
- Impaired production of clotting factors, leading to prolonged prothrombin time. Impaired hepatic metabolism of drugs and endogenous toxins and even may lead to hepatic encephalopathy.
- Gastrointestinal bleeding may develop from alcohol-induced gastritis, esophagitis, and duodenitis. Other causes of massive bleeding in chronic ethanol toxicity involve Mallory-Weiss tears of the esophagus and ruptured esophageal varices. Acute pancreatitis is a common cause of abdominal pain and vomiting in cases of chronic alcoholic toxicity.
- Cardiac disorders involve various cardiac dysrhythmias, such as atrial fibrillation, that may be associated with potassium and magnesium depletion and poor caloric intake ("holiday heart"). Alcoholic cardiomyopathy has been associated with long-term alcohol use. (Cardiomyopathy was also historically associated with ingestion of cobalt ingredient used to stabilize beer.)
- Neurologic toxic manifestations involves cerebral atrophy, cerebellar degeneration, and peripheral stocking-glove sensory neuropathy.
- Nutritional disorders such as thiamine (vitamin B1) deficiency can develop Wernicke encephalopathy or Korsakoff psychosis in cases of chronic alcoholism.

Alcoholic ketoacidosis

- Alcoholic ketoacidosis is a pathological condition that characterized by anion gap metabolic acidosis and elevated levels of beta-hydroxybutyrate and, to a lesser extent, acetoacetate. The osmolar gap may also be elevated, causing this clinical condition to be diagnostic mistaken for methanol or ethylene glycol poisoning.

Alcohol withdrawal.

- Sudden stoppage after chronic high-level alcohol use often develop headache, tremulousness, anxiety, palpitations, and insomnia. Brief, generalized seizures may develop, usually within 6-12 hours of dropped

ethanol consumption. Sympathetic nervous system overactivity may progress to delirium tremens, a life-threatening condition characterized by tachycardia, diaphoresis, hyperthermia, and delirium, which usually manifests 48-72 hours after cessation of heavy alcohol use. The "DTs" may develop high morbidity and mortality rates if untreated.

Other problematic situations.

- Alcoholic abusers sometimes intentionally or accidentally ingest ethanol substitutes, such as isopropyl alcohol, methanol, and ethylene glycol.
- Disulfiram use can cause a severe acute reaction with recurrent ethanol ingestion.

INVESTIGATIONS

General Tests:

- Suggested laboratory tests in the acutely intoxicated alcoholic case may include glucose, electrolytes, BUN, creatinine, hepatic enzymes, prothrombin time (PT/INR), magnesium, arterial blood gases or oximetry, and chest radiography (if pulmonary aspiration is suspected). Ordered CT scan of the head if the case has focal neurologic deficits or altered mental status inconsistent with the level of blood alcohol elevation.

Specific Tests:

- **Serum ethanol levels**
  - Serum ethanol concetration are usually available at most hospital laboratories.
  - Note that serum ethanol levels are approximately 12-18% higher than corresponding blood ethanol levels.
  - Generally, there is only rough relationship between blood ethanol levels and clinical alcoholic presentation; however, an ethanol level below 300 mg/dL in a comatose patient should initiate a search for alternative causes for the disturbed consciousness level condition.

TREATMENT

Emergency and supportive procedures

Acute intoxication.

Mainly supportive treatment.

- Protect the airway to prevent aspiration and intubate and assist ventilation if required.
- Give glucose and thiamine, and treat coma and seizures if they develop. "As in general toxicology section"

- Glucagon is not effective drug for alcohol-induced hypoglycemia.
- Correct alcoholic induced hypothermia with gradual rewarming.

Alcoholic ketoacidosis.

- Treat with volume replacement, thiamine, and supplemental glucose. "General toxicology and antidote sections".
- Most cases recover rapidly.

Alcohol withdrawal.

- Manage with benzodiazepines (eg, diazepam, 2-10 mg IV initially and repeated as indicated) and/or phenobarbital therapy.

Antidotes.

- There is no available specific ethanol receptor antagonist despite anecdotal documents of powerful arousal effect after administration of naloxone therapy.

Decontamination procedures.

- Ethanol is rapidly absorbed from GIT, so gastric decontamination is usually not indicated unless other medication co-ingestion is suspected. Instruct aspirating gastric contents with a small, flexible tube if the ethanol ingestion incidence was massive and recent (within 30-45 minutes).
- Activated charcoal does not effectively adsorb ethanol but may be administrated if other medication or toxins were co-ingested.

Enhanced elimination procedures.

- Excretion of ethanol normally occurs at a fixed rate of approximately 20-30 mg/dL/h.
- Execratory rates are faster in chronic alcoholism cases and patient with serum levels more than 300 mg/dL.
- Hemodialysis procedure efficiently removes ethanol, but enhanced removal is rarely required because supportive care in such cases is usually sufficient.
- Hemoperfusion and forced diuresis procedures are not effective in ethanol toxicity.

FOLLOW UP

Patient monitoring

- Pediatric observation for accidental alcoholic toxicity until their blood alcohol concentration is below 50 mg/dL and there is no evidence of hypoglycemia is mandatory.

Expected course and prognosis

- Most cases alcoholic intoxicate cases will recover within 4-6 hours.

PITFALLS

- Diagnosis of alcohol toxicity is usually simple, based on the history of ingestion, the characteristic smell of fresh alcohol or the rotten odor of acetaldehyde and other metabolic products, and the noticed of nystagmus, ataxia, and altered mental status. However, other medical disorders may associate or mimic alcoholic toxicity, such as hypoglycemia, head trauma, hypothermia, meningitis, Wernicke encephalopathy, and toxicity with other medications or poisons.

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HOUSEHOLD PRODUCTS

CAUSTICS

INTRODUCTION:

- Caustics and corrosives result in tissue injury by a chemical reaction. The majority of caustic substances are either acidic or alkaline. The degree of tissue injury from acidic and alkaline substances is influenced by several factors such as, the duration of contact with the tissues, the amount and state (liquid, solid) of the substance involved. Other physical factors include the pH, concentration and the ability to penetrate the tissues. The alkaline drain cleaners and the acidic toilet bowl cleaners are responsible for the most fatalities from corrosive agents.

TOXIC DOSE:

- Variable: The toxic dose varies tremendously by type and concentration of acid.

EPIDEMIOLOGY:

- Poisoning is common.
- Toxic effects following exposure are typically mild.
- Mortal effects (deaths) occurs after ingestion of a large amount of dilute solution or a smaller amount of concentrated, highly acidic/alkaline compounds.
- Occupational effects (exposure) to acid/alkalies mists are associated with laryngeal cancer.

CAUSES:

- Toxic ingestion is usually accidental in children.
- Adult toxicity is most likely to result from suicidal or occupational exposure.

MECHANISM OF TOXICITY:

- Caustics are typically classified as acids or alkalis. An acid is a proton donor and causes significant tissue injury when the pH < 3. An alkali is a proton recipient and causes significant tissue injury when the pH > 11.
- Acids cause coagulative necrosis. Hydrogen ions desiccate epithelial cells, causing oedema, erythema, tissue sloughing, and necrosis, with the formation of ulcers and eschars.
- Alkalis cause liquefactive necrosis, a process that involves saponification of fats and protein dissolution. Cell death occurs as a result of

emulsification and disruption of cellular membranes. The hydroxide ion in alkaline agents reacts with tissue collagen and causes it to swell and shorten. Small vessel thrombosis and heat production occur.

CLINICAL MANIFESTATIONS:

- Signs and symptoms of impending airway irritation or obstruction: Dyspnea, stridor, hoarseness, dysphonia or aphonia, respiratory distress, tachypnea, hyperpnea, cough and chest pain.
- Other symptoms and signs of injury: Nausea, vomiting, oropharyngeal burns (pain or swelling) these are important when identified. However, significant esophageal damage may occur even in the absence of oropharyngeal lesions. Other symptoms include, drooling, dysphagia, abdominal pain, subcutaneous air, hematemesis, melena, tachycardia, acute peritonitis (abdominal guarding), rebound tenderness, and diminished bowel sounds.
- Signs of severe injury: Altered mental status, peritoneal signs, perforation, hypotension, stridor, renal failure, electrolyte disturbance, metabolic acidosis, hemolysis, and shock.

DIFFERENTIAL DIAGNOSIS:

- Chemical Burns - Thermal burns - Dysphagia
- Gastrointestinal hemorrhage or perforated viscus.

INJURY SEVERITY AND COMPLICATIONS:

Grade	Findings	Comments
Grade 0	No injury	No adverse effects
Grade I	Erythema, edema	No adverse sequelae
Grade IIa	Limited to mucosa	No adverse sequelae
Grade IIb	Blister, ulceration and whitish membrane penetrating the mucosa	May develop strictures
Grade III	Extensive necrosis, full thickness or frank perforation	High morbidity and mortality may result in perforation, mediastinitis, or peritonitis. Strictures are seen in the majority.

INVESTIGATIONS:

Routine:

- Bed Side RBS.
- ABGs, Electrolytes.
- CBC, BUN, Creatinine, ALT, AST, Creatine Kinase.
- EKG.
- Pregnancy test for females at childbearing period.

Specific:

- Determine type and cross match for blood, and monitor urine output.
- Serum lactate and base deficit are useful prognostic tools.
- MetHb levels, LDH for (phenol), calcium for (oxalates, fluorides) and urine oxalate.
- Chest X-ray is performed to evaluate for pneumo-mediastinum or free air under the diaphragm. The absence of these findings DOES NOT rule out the possibility of necrosis or perforation of the esophagus or stomach.
- Abdominal x-ray findings to evaluate for pneumoperitoneum, ascites, or an ingested button battery (metallic foreign body).
- CT scan is useful in the detection of small amounts of extraluminal air not caught on plain radiographs.
- Several weeks after ingestion, barium contrast X-rays of the upper GI tract are useful in patients with grade II or III burns to evaluate for strictures.

TREATMENT:

Stabilization:

- Airway, breathing, and circulation (ABC) should be evaluated and stabilized as necessary.
- Nothing per oral (NPO) and IV fluids till complete evaluation.
- Do not force the patient to vomit or drink.
- Allow the patient to drink a small amount of water if able to drink for the purpose of checking for ability to swallow.

Decontamination:

- In ocular burn rinse with 0.9% sodium chloride or running tap water 30-32 °C for 15 min followed by emergency ophthalmologic consultation.
- In dermal burn: Remove contaminated clothes, brush off particulate corrosives, and follow with copious irrigation.

Specific:

Endoscopy:

- It should be performed as soon as possible (best if within 12 hrs and not more than 24 hrs) in any patient who ingested high volumes of a caustic substance. The grade of mucosal injury at endoscopy is the strongest predictive factor for the occurrence of complications and mortality. The absence of visible oral burns and oedema does NOT reliably exclude the presence of esophageal or gastric burns.
- In patients in whom endoscopy reveals extensive circumferential burns (grade IIB or III), a nasogastric tube (NGT) should be placed under direct visualization during the endoscopic procedure. A NGT should not be inserted blindly to avoid perforation, or additional injury that can occur while passing the tube. The NGT can provide a route for nutritional support during the healing phase and help maintain a lumen during stricture formation. It can serve as a useful guide for esophageal dilatation. Consider a useful radiological control 30 days after the ingestion and an endoscopy 4-6 weeks after the ingestion.
- Consult an otolaryngologist if stridor did not improve for possible tracheostomy.
- Consult a surgeon and perform abdominal X-ray & amylase if the patient experienced rebound tenderness, rigidity or severe abdominal pain.

Supportive treatment:

- Analgesia with paracetamol, NSAIDs and morphine are permitted initially. H2 blockers or proton pump inhibitors IV infusion (0.7-3.5 mg/kg/day).
- Bronchospasm: Treat with oxygen, inhaled β agonists and consider systemic corticosteroids. Consider mechanical ventilation if ventilation is compromised.
- Blood transfusion if Hb is less than 8 gm/dl or rapid hemorrhage reducing Hb to < 80% of expected value.
- IV fluid followed by total parenteral nutrition (TPN) if stage II or III corrosion or severe dysphagia or respiratory compromised (inability to cough). Refer to TPN protocol.
- Antibiotics should be used when indicated.
- Steroids: The use of corticosteroids to prevent stricture formation is controversial.

- Oral fluids then liquid diet may be permitted only with caution if endoscopy was not performed, and the patient does not complain from dysphagia or respiratory complications. The oral diet should be stopped if vomiting or bleeding occurred.
- Observe for evidence of bleeding (e.g. hematemesis, melena), nutritional status and respiratory function.
- Observe for broncho-esophageal fistula that can form on the 7^{th}-10^{th} day by imaging (cough on drinking).
- Refer to surgery department for treatment and follow-up of any possible complications from caustic injury.

Admission Criteria:

- Symptomatic patients and those with endoscopically confirmed grade II or higher burns should be admitted.
- Patients presenting with respiratory distress, grade III burns, or extensive grade II burns, metabolic acidosis, hemodynamically unstable, gastrointestinal bleeding, or large ingestions should be admitted to an intensive care setting.

COMMON PITFALLS:

- Diluting the corrosive by excessive drinking of water or milk as they may induce vomiting.
- Neutralizing the corrosive.
- Administration of syrup ipecac and performing gastric lavage.
- The use of activated charcoal as it is not effective and potentially hazardous.
- Insertion of Ryle tube blindly unless endoscopically guided.
- Blind naso or endotracheal intubation.
- The absence of oral burns does NOT reliably exclude the possibility of significant esophageal burns.
- Patients may have severe tissue necrosis and impending perforation requiring early surgical intervention without having severe hypotension, rigid abdomen, or radiographic evidence of intraperitoneal air.
- Patients with any evidence of upper airway involvement require early airway management before airway edema progresses.
- The extent of eye injury (degree of corneal opacity) may not be apparent for 48-72 hours after the burn.

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HYDROCARBONS

INTRODUCTION:

- Hydrocarbons are organic substances that possess carbon and hydrogen atoms. At room temperature they are usually in liquid form. Kerosene, gasoline, mineral seal oils, and naphtha are examples of hydrocarbons. Hydrocarbons are often mixed with agents such as camphor, aniline dyes, heavy metals, and pesticides. These agents can produce systemic toxicity.
- Types of hydrocarbons: Aliphatic, aromatic, halogenated, metal additives, pesticide additives and camphor. When history of hydrocarbon exposure is lacking, characteristic odors can help.

FORMS AND USES:

- Aliphatic hydrocarbons (straight-chain molecules)
  - Short-chain forms include methane, ethane, propane, and butane.
  - Longer chain molecules are pentane, hexane, heptane, and octane.
- Cyclic hydrocarbons
  - Bitumens, creosotes, gasoline, kerosene, mineral seal oil, motor oil, naphtha, petroleum, shole oils, soots, Stoddard solvent, and other products are mixtures of various hydrocarbons, which usually do not include active functional groups such as halogens (chloride, fluoride).
- Organic hydrocarbon solvents are used for extracting, dissolving, or suspending materials, such as fats, waxes, and resins that are not soluble in water.
- Solvents are components of paints, adhesives, glues, coatings, and degreasing/cleaning agents, and are used in the production of dyes, polymers, plastics, textiles, printing inks, agricultural products, and pharmaceuticals.

TOXIC DOSE:

- Aspiration of just a few drops can cause aspiration pneumonitis.
- Conversely, ingestion requires large amounts to produce serious toxicity, unless the hydrocarbon product contains other toxins (halogens, pesticides).

EPIDEMIOLOGY:

- Hydrocarbon poisoning is common.
- Toxic effects following exposure are typically mild to moderate.
- Death is rare and usually associated with pulmonary aspiration.

CAUSES:

- Hydrocarbon poisoning is usually accidental.

WORKPLACE STANDARDS:

- Gasoline. ACGIH: TLV TWA is 300 ppm; STEL is 500 ppm.
- Hexane. ACGIH (n-hexane): TLV TWA is 50 ppm. NIOSH (n-hexane): REL TWA is 50 ppm; IDLH is 1100 ppm. OSHA: PEL TWA is 500 ppm.

MECHANISM OF TOXICITY:

- Pneumonitis is common after aspiration of hydrocarbons. The specific mechanism of pulmonary toxicity is still not clear but is likely to be as a result of direct toxicity to the lung tissue in addition to destruction of the surfactant.
- Chlorinated hydrocarbons may increase cardiac sensitization to catecholamines which in turn produces cardiac dysrhythmias.
- The specific mechanism of CNS depression from hydrocarbon poisoning is unclear. Halogenated hydrocarbons may also cause hepatotoxicity, nephrotoxicity, and electrolyte disturbances.

CLINICAL MANIFESTATIONS:

- Vital signs: Fever starts at the time of presentation (38-40°C). Persistence of fever beyond 48 hrs. Suggests bacterial superinfection. Pulse oximetry may reveal decreased oxygen saturation.
- Respiratory: Signs of aspiration include coughing, choking, gagging, and vomiting.
  - Signs of respiratory distress tachypnea, dyspnea, cyanosis, wheezing, diminished resonance on percussion, suppressed or tubular breath sounds, rales, nasal flaring, and/or grunting respirations.
  - Major pulmonary complications include asphyxia, necrotizing chemical pneumonitis, lipoid pneumonia, and hemorrhagic pulmonary edema. These complications can rapidly progress to shock and respiratory arrest. Pneumothorax, subcutaneous emphysema of the chest wall, and pleural effusion, including empyema.
- CNS: Somnolence, headache, ataxia, dizziness, blurred vision, weakness, fatigue, lethargy, stupor, seizures, and coma, depending on the amount ingested. In addition, hypoxia caused by hydrocarbon aspiration may cause secondary CNS toxicity, including drowsiness, tremors, or seizures.

- Cardiovascular: Cardiac dysrhythmias and myocardial dysfunction.
- Gastrointestinal: Ingestion of aliphatic hydrocarbons causes direct local irritation, which may be associated with nausea, vomiting, and hematemesis.
- Hepatic and/or renal tubular necrosis: May be caused by halogenated hydrocarbons.
- Hematologic: Leukocytosis, which occurs early unrelated to pneumonitis, hemolysis, hemoglobinuria, and consumptive coagulopathy.

DIFFERENTIAL DIAGNOSIS:

- Hypoglycemia, CNS infection, pulmonary infection, rheumatologic or endocrine etiology, poisoning with sedatives e.g. ethanol/ benzodiazepine/barbiturate for example, mental illness.

INVESTIGATIONS:

Routine:

- Bed Side RBS.
- ABGs, Electrolytes.
- CBC, BUN, Creatinine, ALT, AST, Creatine Kinase.
- EKG.
- Pregnancy test for females at childbearing period.

Specific:

- Chest X-ray in cases with any respiratory symptoms to be performed after 12hr from ingestion. (Note: The chest radiograph may be normal early in the clinical course)
- EKG and continuous cardiac monitoring in patients with moderate to severe toxicity or chlorinated hydrocarbon exposure.
- Monitor ABG, pulse oximetry, and pulmonary function tests.
- Suspect methemoglobinemia in cyanotic patients who do not show adequate response to supplemental oxygen, and who may have been exposed to nitrobenzene or aniline containing hydrocarbons.
- Head CT should be obtained in patients with altered mental status.
- ABG findings: Initial blood gases commonly show mild respiratory alkalosis with hypoxemia.
- If hypoxemia is not corrected, the patient will later develop metabolic acidosis.
- Chest radiographic findings: Initial radiographic findings consist of

multiple, small, patchy densities with ill-defined margins. The lesions become larger and coalesce as the injury progresses. The lesions rapidly progress to extensive infiltrates. Emphysema or pneumothorax may develop.

Admission criteria:

- Symptomatic patients and patients with suicidal intent or massive ingestion.
- Indications for admission during observation include:
  - Patients with normal or mildly abnormal initial chest radiograph who develop symptoms.
  - Patients who develop symptoms related to toxic additives (e.g., heavy metals or OPI).
  - Patients with mild symptoms and normal chest radiograph who fail to improve.
- Admit to I.C.U: Patients with CNS manifestations as coma, dysrhythmias, or respiratory distress.
- Indications for discharge after 6 hrs of observation include:
  - Asymptomatic patient with normal chest radiograph.
  - Asymptomatic patient with mildly abnormal chest radiography who does not develop symptoms during the observation period and who can follow-up in the next day

TREATMENT:

Asymptomatic Patients:

- Perform serial examination with monitoring. These patients should refrain from oral feeding (NPO) during the initial observation period.
- Discharge if the patient remains asymptomatic for 6 hrs.
- If the patient becomes symptomatic, initial radiographic evaluation should be performed after 12 hrs.

Symptomatic Patients:

Stabilization:

- ABCs: Airway is always the first priority of treatment in patients with hydrocarbon poisoning. Administer supplemental oxygen to all patients, and perform beside pulse oximetry.

Decontamination:

- Cutaneous decontamination in cases of cutaneous exposure: Decontaminate the skin as soon as possible by removing the involved

clothing and thoroughly washing the skin with soap and water.

- Don't use syrup of ipecac, gastric lavage or activated charcoal.

Supportive treatment:

- Supplemental O_2 to maintain O_2 saturation > 94%.
- Administer β-agonist bronchodilators (e.g, Albuterol) for bronchospasm.
- Administer benzodiazepine (e.g, Lorazepam 0.1 mg/kg) for seizures in addition to support of airway and breathing.
- Dysrhythmias: Initiate ACLS protocol. Epinephrine and other sympathomimetics should be used with caution as ventricular dysrhythmias may be precipitated.
- In severe respiratory distress, consider the use of surfactant (Infasurf®) 3mL/kg intratracheally.
- In patients with respiratory failure: Partial liquid ventilation, high frequency jet ventilation, extracorporeal membrane oxygenation (ECMO) and high frequency chest wall oscillation have all been used with apparent success in cases of severe hydrocarbon pneumonitis.
- Prophylactic use of antibiotics, or corticosteroids should be avoided with hydrocarbon pneumonitis. Antibiotics used only with signs of secondary bacterial infection. These signs include:
    - Recurrence of fever after the first 48 hrs.
    - Increasing infiltrate in chest radiography.
    - Leukocytosis after the first 48 hrs.
    - Sputum or tracheal aspirate is positive for bacteria.

FOLLOWUP:

Patient Monitoring

- Cardiac and respiratory function should be monitored continuously.
- Expected Course and Prognosis
- Respiratory system toxicity may develop within hours of acute pulmonary aspiration.
- Recovery from ingestion is usually rapid unless aspiration occurs.
- The prognosis of inhalation or aspiration depends on the degree of pulmonary injury.
- Systemic poisoning is possible from pulmonary absorption.
- Permanent CNS, pulmonary, or hepatic damage is possible in severe cases, especially if complicated by hypoxia.

Discharge criteria and Instruction

- Patients with normal vital signs who are asymptomatic may be discharged from the emergency department or the hospital following decontamination and 6-hour observation.

COMMON PITFALLS:

- Failure to aggressively manage the airway can result in death.
- Patients with minimal respiratory symptoms may progress to severe toxicity over several hours.
- Patients with altered mental status should be ruled out for intracranial hemorrhage, infection, metabolic disturbance and other toxicological causes.

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METHANOL

INTRODUCTION:

- Methanol poisoning causes fatal intoxications, and even relatively small ingestions of this alcohol can produce significant toxicity. Rapid identification of toxicity and early management, are crucial.
- Methanol is frequently found in high concentration in antifreeze and de-icing solutions, windshield wiper fluid, solvents, cleaners, fuels, and other industrial products. Most serious poisonings occur following ingestion. Toxicity is most common after oral intake but has also been reported after inhalation and dermal exposures.

Toxic dose:

- Oral intake of approximately 1 gm/kg of methanol is considered lethally toxic. Severe toxicities from methanol have been reported following ingestions of as little as one teaspoon.

MECHANISM OF TOXICITY:

- Methanol is metabolized to formaldehyde and formic acid via alcohol dehydrogenase and aldehyde dehydrogenase, respectively.
- Formic acid produces a significant anion gap metabolic acidosis and causes blindness through direct injury to the optic nerve and retina. Additionally, formic acid causes ischemic or hemorrhagic injury to the basal ganglia. Metabolic acidosis increases the ability of the toxic metabolites to penetrate the cells.

CLINICAL MANIFESTATIONS:

Mild to moderate toxicity:

- Ataxia, sedation, and disinhibition.
- Patients may present with abdominal pain, nausea, vomiting, and headache.

Severe toxicity:

- Severe metabolic acidosis develops 6-12 hrs after intake (if ethanol is not co-ingested) and may lead to multiorgan dysfunction including hypotension, tachycardia, dysrhythmias, seizures, coma, pancreatitis, and acute renal failure.
- Ocular toxicity may develop; manifestations include mydriasis, hyperemic optic discs, and papilledema. Visual impairment may develop, which may range from blurry/hazy vision to color vision

defects to "snowfield" vision to total blindness. Rhabdomyolysis may occur in severe poisonings.

- Hypomagnesemia, hypokalemia, and hypophosphatemia have also been reported.
- Permanent sequelae after severe intoxication may include basal ganglia necrosis with parkinsonian features (i.e., tremor, rigidity, bradykinesia) and blindness.

Admission Criteria:

- Patients who are acidotic, have visual symptoms, or have serum methanol concentrations above 25 mg/dL should be admitted.

DIFFERENTIAL DIAGNOSIS:

- Exposure to other alcohols, such as ethanol, ethylene glycol, isopropyl alcohol, and other glycol ethers.
- Other causes of metabolic acidosis.

INVESTIGATIONS:

Routine:

- Bed Side RBS.
- ABGs, Electrolytes.
- CBC, BUN, Creatinine, ALT, AST, Creatine Kinase.
- EKG.
- Pregnancy test for females at childbearing period.
- Calculate the anion gap and osmolar gaps. An elevated osmolal gap (> 10) suggests the presence of toxic alcohols, but a normal osmolal gap does NOT rule methanol toxicity.

Specific:

- Measurement of serum methanol, ethylene glycol, and ethanol levels.
- Check urine ketones and urine sediment for calcium oxalate.
- Urine ketone (acetone) without acidosis may point to isopropanol contamination.
- Test for alcohol in gastric aspiration.
- Request fundus examination for any ocular or visual complaint.
- Request brain CT or MRI for probable delayed necrosis of basal ganglia (putamen and less commonly caudate nucleus) especially for patients with EKG ischemic signs. An early cerebral oedema may be noted.

- Urine ketone (acetone) without acidosis may point to isopropanol contamination.
- Rising creatinine, hypocalcemia, increased QTc, increased WBC, and calcium oxalate crystals in urine favor the possibility of ethylene glycol contamination.

TREATMENT:

- A Rapid decision is critical in the management of the patient poisoned with methanol. The clinician must often make treatment decisions without definitive serum drug levels, based only upon history, clinical suspicion and available laboratory data.
- A diagnosis of methanol poisoning is made if visual complaint is associated with severe metabolic acidosis (even if partially compensated) following alcohol ingestion, even if serum methanol level is not available.

Stabilization:

- ABC: Secure the patient's airway, breathing, and circulation, and provide appropriate supportive care.
- Endotracheal intubation may be necessary for patients with significant CNS or respiratory depression. Extreme care must be taken to increase minute ventilation sufficiently to prevent severe acidemia in intubated patients.

Decontamination:

- There is no role for activated charcoal (AC), gastric lavage, and syrup of ipecac in the management of toxic alcohol exposures.

Antidotes:

- Inhibition of the alcohol dehydrogenase enzyme: with either fomepizole (preferred) or Ethanol (if fomepizole is unavailable)

Indications:

- Plasma methanol concentration greater than 20 mg/dL.
- A documented recent history of ingesting toxic amounts of methanol and osmolal gap greater than 10 mOsm/L.
- History or strong clinical suspicion of methanol poisoning with at least 2 of the following criteria:
  - Arterial pH < 7.3.
  - Serum bicarbonate < 20 mEq/L.
  - Osmolal gap > 10 mOsm/L.

Dose:

- Fomepizole: Loading dose: 15 mg/kg over 30 min, followed by 10 mg/kg q 12 hrs for 4 doses, then if necessary, 15 mg/kg q 12hrs until blood pH is normal, and serum alcohol concentration < 20 mg/dL.
- Ethyl alcohol if fomepizole is absent
  - Ethyl alcohol: Intravenous form loading dose (0.8 gm/kg, 8 mL/kg of 10% ethyl alcohol infused over 1 hour as tolerated). Maintenance Dose is 110 mg/kg/hr = 11 mL/kg/hr.
  - In chronic alcoholism 150 mg/kg/hr = 15 mL/kg/hr.
  - During hemodialysis 250 mg/kg/hr = 30 mL/kg/hr.

Ethanol oral form:

- Loading dose 0.8 gm/kg = 4mL/kg of 20% ethanol ingested over 1 hr added to juice.
- Maintenance dose is 110 mg/kg/hr = 6 mL/kg/hr.
- In chronic alcoholism 150 mg/kg/hr = 8 mL/kg/hr
- During Hemodialysis: 250 mg/kg/hr.

Supportive treatment:

- Administer sodium bicarbonate to correct the systemic acidosis, which limits the penetration of toxic acids (e.g., formic acid) into end-organ tissues such as the retina. Dose: Initial dose 1-2 mEq/kg of sodium bicarbonate via IV bolus for any patient with a pH < 7.3. The bolus dose is then followed by a maintenance infusion prepared by mixing 133 mEq of sodium bicarbonate in 1 liter of D5W. This mix is then infused at a rate of 150-250 mL/hr in adults, or one to two times the maintenance fluid rate in children. The appropriate rate depends upon the initial pH, and such parameters as fluid status and serum sodium concentration. The goal of treatment is maintenance of pH > 7.35.
- Closely observe for respiratory rate, level of consciousness, hypokalemia and volume overload during NaHCO3 treatment.
- Treating with cofactors: (Folic acid, thiamine, and pyridoxine) to optimize non-toxic metabolic pathways for the elimination of the alcohol or its metabolites.
- Administer intravenous folic acid or folinic acid 50 mg every 6 hrs for the first 24 hrs, and should be continued until the methanol and formate are eliminated.

- Thiamine (100 mg IV/day) or pyridoxine (50 mg IV).
- Hemodialysis: is indicated in the setting of known methanol ingestion if any of the following conditions is present:
    - High anion gap metabolic acidosis (>10), regardless of drug level.
    - Evidence of end-organ damage (e.g., visual changes and renal failure).
    - In any patient with a suspected toxic alcohol ingestion and has severe unexplained anion gap metabolic acidosis and significant plasma osmolal gap.
    - Methyl alcohol concentrations greater than 50 mEq/L, even in the absence of acidosis or severe symptoms.
        - Hemodialysis should be continued until the methanol concentration is undetectable, and the serum pH returns to normal.
    - Check potassium and methanol levels after each hemodialysis session and correct hypokalemia.
    - Avoid hypoglycemia, hyponatremia, hypokalemia by regular dextrose and electrolyte infusion.
    - Add H2 blocker or proton pump inhibitors.

COMMON PITFALLS:

- Depending on the timing of the presentation, an increased osmolar gap or an increased anion gap may not always be present. An increased anion gap will not be present in patients presenting early, and an increased osmol gap may not be present in patients presenting late.
- When calculating osmolarity, the ethanol level needs to be taken into account in the calculation.
- A normal osmolal gap does not rule out the possibility of methanol intoxication.
- Patients who are ethanol intoxicated will have a later presentation of their acidosis.

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PARAPHENYLENEDIAMINE

(HAIR DYE)

INTRODUCTION:

- Paraphenylene diamine (PPD) is a dark-coloured hair dye. Sometimes, it added to henna (*Lawasonia alba*), as a dye to decorate the palms of the hands and soles of the feet.
- Toxicity occurs through skin absorption. Yet, systemic toxicity occurs when it is accidentally or intentionally ingested.
- The lethal dose for humans is estimated to be 10 grams of pure PPD while 2- 3 grams can cause severe toxic effects.

MECHANISM OF TOXICITY:

- Paraphenylene diamine is a derivative of paranitroanaline. Upon oxidation of Paraphenylene diamine, several intermediate compounds are produced. However, the most toxic compound produced is the Bondrowski's base which is a highly allergenic and toxic compound. If applied topically or ingested, it produces local as well as systemic toxic effects. It is highly toxic when ingested orally and the outcome depends mainly on the dose consumed.
- The main clinical manifestations include angioedema leading to dysphasia and respiratory distress, rhabdomyolysis, intravascular hemolysis, acute renal failure and hepatic necrosis. PPD poisoning may also result in myocarditis or fatal arrhythmia.

CLINICAL MANIFESTATIONS:

- The onset of symptoms usually occurs within 1-2 hrs. of ingestion or contact with the dye.
- Patients with acute poisoning have a characteristic presentation of painless swelling of the face and neck often requiring urgent tracheostomy, with bulging eyes, a swollen dry hard protruding tongue and chocolate brown color of the urine.
- PPD is a poison the affects multiple organs and could result in severe muscular pain due to rhabdomyolysis. It can also cause acute renal failure (ARF), flaccid muscle paralysis, severe gastro-intestinal symptoms, cardiotoxicity and arrhythmias.
- Severe toxicity could be fatal if not treated promptly.
- Cardiac arrest is the main cause of death and it is attributed to arrhythmia.

INVESTIGATIONS:

- **Routine:**
  - Bed Side RBS.
  - ABGs, Electrolytes.
  - CBC, BUN, Creatinine, ALT, AST, Creatine Kinase.
  - EKG.
  - Pregnancy test for females at childbearing period.
- **Specific:**
  - Urine is tested for myoglobin and PPD using chromatographic techniques for confirmation of intoxication and medico-legal purposes.

TREATMENT:

- **Stabilization:**
  - Assess airway, breathing, and circulation; stabilize as necessary.
- **Decontamination:**
  - Oral *exposure*: Prehospital gastrointestinal decontamination is generally not recommended because of the potential for CNS depression or persistent seizures and subsequent aspiration.
- **Inhalational exposure:**
  - Monitor for signs of respiratory distress. If the patient exhibits severe persistent cough or breathing difficulties, administer oxygen and assist ventilation as required.
  - Treat bronchospasm with a β2-adrenergic agonist inhaler.
  - Administer systemic corticosteroids in patients with significant bronchospasm.
- **Dermal exposure:**
  - Remove contaminated clothing and wash exposed area thoroughly with soap and water.
- **Eye exposure:**
  - Remove contact lenses (if present) and irrigate exposed eyes for 15 minutes with large amounts of normal saline or water. A thorough ophthalmologic examination is warranted if irritation, lacrimation, pain, swelling, or photophobia persists after 15 minutes of eye irrigation.

- **Supportive treatment:**
  - Administer hydrocortisone 4-8 mg/kg/dose initially then 2-4 mg/kg/dose 6 hourly for 48-72 hrs. for the severe hypersensitivity reaction, the angioedema and as an anti-inflammatory.
  - Give Chlorpheniramine maleate 0.25-5 mg/kg/dose in children less than 5 years and 5-10 mg/kg/dose in children more than 5 years. Dose can be repeated 4 hourly for up to 24 hrs. if needed.
  - Refer the patient to the Otolaryngology department if facial edema is increasing.
  - Acute renal failure was found to be the second life-threatening effect. Contact nephrology unit for hemodialysis, peritoneal dialysis and/or haemoperfusion.
- **Indications of intubation:**
  - Moderate or severe respiratory distress.
  - ABG abnormalities; PaO2 < 60 on 6 liters O2 or PaCO2 > 50mmHg.
  - Deterioration in mental status.
  - Absence of breath sounds.
  - Cyanosis on 40% FiO2.
  - Exhausted patient with decreased respiratory effort.

Asymptomatic cases with normal vital signs need close observation and monitoring for at least 72 hrs.

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PESTICIDES POISONING

ALUMINUM AND ZINC PHOSPHIDE

INTRODUCTION:

- For many years, aluminum and zinc phosphide have been highly effective insecticides and rodenticides with the major merits of being inexpensive and not leaving toxic residue. They are formulated as compressed discs, tablets or pellets that commonly weigh 3 gms and contain variable amounts of a single phosphide combined with other substances such as ammonium carbonate.
- It should be noted that phosphine could be released as a gas from emesis, faeces, or lavage material. Thus, these materials should be disposed of in closed containers. However, serious toxicity in health care providers caring for patients poisoned with metallic phosphides has not been described. The management of phosphide ingestion is based upon limited evidence derived from case reports.

MECHANISM OF TOXICITY:

- Several mechanisms of toxicity have been proposed, including inhibition of oxidative phosphorylation, free radical production with the promotion of lipid peroxidation, and cholinesterase inhibition but none fully explain the clinical features of poisoning. Mortality often occurs rapidly within the first day of severe metallic phosphide poisoning regardless of therapy. Death typically results from cardiac arrhythmias or refractory shock and cardiac failure.

CLINICAL FEATURES:

GI manifestations:

- Smell of garlic in breath (common).
- Nausea and vomiting.
- Retrosternal and epigastric pain.
- GI bleeding.
- Diarrhea (less common).

Metabolic and Electrolyte disturbances (Cause early mortality):

- Metabolic acidosis, or mixed metabolic acidosis and respiratory alkalosis are frequent.
- Hypoglycemia has been reported and may be persistent and severe, but rare.

CVS manifestations (Cause early mortality)

- Shock and peripheral circulatory failure are particularly important early signs of toxicity.
- Tachycardia, bradycardia or cardiac arrhythmias (all types of arrhythmias have been recorded.

Respiratory Manifestations:

- Tachypnea, dyspnea.
- Hemorrhagic pulmonary oedema (could be cardiac or respiratory in origin) could take up to 48 hours to develop, crepitations and rhonchi.

Hepatic Manifestations: (Tends to occur late in the course of illness)

- Elevation of ALT and AST.
- Elevation in levels of bilirubin has been recorded in a few cases.

Renal Manifestations:

- Acute renal failure.

CNS manifestations:

- Anxiety and agitation are common while mentally clear.

INVESTIGATIONS:

Routine:

- Bed Side RBS to exclude hypoglycemia
- ABGs and Electrolytes (Na, K, Ca, Mg.)
- BUN, Creatinine, ALT, AST, Creatine Kinase.
- Serum Paracetamol and Salicylates.
- EKG.
- Pregnancy test for females in childbearing period.

TREATMENT:

Early consultation with a poison control center or medical toxicologist is advised for all patients.

Stabilization:

- Health care providers should take all necessary precautions to protect themselves from exposure to phosphine gas while providing care for patients with suspected aluminum or zinc phosphide ingestion.
- Hypoglycemia, hypokalemia, hypocalcemia and hypomagnesemia are common and should be monitored and corrected

promptly. In some cases, correction of hypokalemia can reverse cardiac manifestations.

- Provide supplemental oxygen and ventilation as needed and dictated by the degree of respiratory compromise. Tracheal intubation may be performed in a standard fashion.
- Provide fluid resuscitation with rapid infusions of isotonic normal saline to replace obvious fluid losses and to treat hypovolemic shock.
- Treat hypoglycemia and correct hypokalemia, hypocalcemia and hypomagnesemia as indicated.
- Treat cardiogenic shock with vasoactive medications as needed in patients unresponsive to isotonic fluid resuscitation.
- Manage atrial and ventricular arrhythmias according to ACLS and PCLS guidelines and consult the cardiologist.

Decontamination: (Limited role)

- Gastric Lavage is not advised, as there are reports that it aids the disintegration of zinc or zluminum phosphide and may increase the production of phosphine.
- Evidence of the efficacy of activated charcoal in limiting the toxicity of zinc phosphide is limited.
- Additional Therapies: Additional therapies have been described, but we strongly encourage consultation with a regional poison control center or a medical toxicologist, whenever possible, before giving these treatments.

Adjunct therapies include the following:

- Magnesium infusion – Case series have documented hypomagnesaemia in some patients poisoned with metallic phosphides. Hypomagnesaemia should be corrected in all patients with metallic phosphide poisoning. Nevertheless, studies of treatment with intravenous magnesium have yielded mixed results.
- Some trials suggest intravenous magnesium administration can decrease mortality if hypomagnesaemia is identified and the regimen chosen raises the magnesium levels. In these trials, the regimen with the best effect was as follows: 1 gm magnesium sulfate, IV followed 1hr later by 1 gm given as a

continuous infusion over 3 hrs and then 1 gm q 6 hours until recovery or a maximum duration of 5 days.

Insulin and dextrose infusion

- Insulin infusion combined with maintenance of normal blood glucose using a continuous dextrose infusion was associated with survival in four of five patients with large ingestions of aluminum phosphide. Thus, this therapy may be beneficial in patients who are not responding to supportive care and who are unlikely to benefit from magnesium infusion.

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ORGANOPHOSPHATES AND CARBAMATES

INTRODUCTION:

- Organophosphates (OPI) (parathion, fenthion, malathion) and carbamates (methomyl and aldicarb) are potent cholinesterase inhibitors that have the ability to cause severe cholinergic toxicity following cutaneous exposure, inhalation, or ingestion.
- Organophosphates and carbamates exhibit similar clinical manifestations and toxicity and require similar management following overdose.
- Organophosphates have been used as insecticides, while carbamates are used in pest control in industrial agriculture to control ectoparasites on farms and companion animals and for home and garden pest control.
- Several organophosphate nerve agents (e. g, tabun [GA], sarin [GB], soman [GD]) are used as chemical weapons.

MECHANISM OF TOXICITY:

- Organophosphates and Carbamates competitively inhibit pseudo-cholinesterase and acetylcholinesterase, preventing hydrolysis and inactivation of acetylcholine. Acetylcholine accumulates at nerve junctions causing malfunction of the sympathetic, parasympathetic, and peripheral nervous systems and some of the CNS. Clinical signs of cholinergic excess can develop.
- There are 4 main pharmacokinetic characteristics that distinguish carbamates from organo phosphate compounds.
  - Carbamates insecticides do not easily cross into the central nervous system (CNS). Thus CNS effects of carbamates are limited, although CNS dysfunction may still occur in massive poisonings or may occur as a result of hypoxia secondary to pulmonary toxicity and paralysis.
  - The Carbamate-cholinesterase bond does not “age” as in organophosphates compound poisoning; thus it is reversible, with spontaneous hydrolysis occurring typically within several hours.
  - Carbamates have rapid onset and short duration of action.
  - Generally carbamates are less toxic than organophosphates. Aldicarb is considered the most toxic carbamates.

CLINICAL MANIFESTATIONS:

Muscarinic:

DUMBBELS (Diarrhea, Urinary incontinence, Miosis, Bradycardia, Bronchorrhea and bronchospasm, Emesis, Lacrimation, and Salivation).

Nicotinic:

Tachycardia, hypertension, muscle cramps, muscle fasciculations, weakness, and respiratory failure.

CNS:

Anxiety, lethargy, confusion, psychosis, convulsions and coma.

Cardiac:

Myocardial ischemia and arrhythmias, including heart block, QTc prolongation and ventricular dysrhythmias, are occasionally observed in OPI agent poisoning.

Others:

Metabolic acidosis, pancreatitis, and hyperglycemia can also develop.

Delayed Toxic Syndromes:

Intermediate (neurologic) syndrome:

Some patients poisoned with OPI develop neurological disorder 24-96 hrs after exposure. This neurological disorder consists of characteristic neurological symptoms that include neck flexion weakness, attenuated deep tendon reflexes, cranial nerve deficits, proximal muscle weakness, and respiratory insufficiency. Recovery begins 5-15 days after onset.

Delayed and long-term neuropathology:

Organophosphates agent-induced delayed neuropathy (OPIDN) typically occurs 1-3 weeks after ingestion of one of a small number of specific OPI agents, including chlorpyrifos.

Affected patients present with transient, painful "stocking-glove" paresthesias followed by an ascending symmetrical motor polyneuropathy that has a characteristic flaccid weakness of the lower extremities, which extends to involve the upper extremities. Survivors of acute organophosphates poisoning may have neurobehavioral deficits.

Admission Criteria:

- All intentional ingestions should be initially managed as a severe exposure.
- Determine cholinesterase activity to assess if a significant exposure occurred.
- Patients who exhibit severe cholinergic manifestations (e.g., muscarinic, nicotinic or central) should be admitted to an intensive care setting.

These patients should be continuously monitored, frequently titrated dosage of antidotes administered, ventilation and inotropes are given as needed. Consult a medical toxicologist and/or poison center.

- Patients should be monitored closely for 48 hrs after discontinuation of atropine and oximes for evidence of recurrent toxicity or intermediate syndromedecreased memory, abstraction, and Parkinsonism which may be permanent.

DIFFERENTIAL DIAGNOSIS:

- Gastroenteritis and food poisoning.
- Asthma, myasthenic crisis, and cholinergic excess from medications.

INVESTIGATIONS:

Routine:

- Monitor serum glucose, serum electrolytes, ABG.
- BUN, creatinine, Hct, and serum lipase in patients with significant poisoning.
- EKG (document QT, rate and rhythm).
- Chest X-ray if respiratory complication (failure, PE, aspiration).

Specific:

- Determine plasma (pseudo) and/or red blood cell (True) cholinesterase activities (plasma is more sensitive, but red cell correlates somewhat better with clinical signs and symptoms). Depression in excess of 50% of baseline is generally associated with cholinergic effects.

TREATMENT:

Stabilization:

- ABCs and O2 (oxygen should be provided at first).
- Promptly assess airway and respiratory function. Administer oxygen and perform sufficient suction of secretions. Endotracheal intubation may be necessary due to respiratory muscle weakness or bronchorrhea. Avoid the administration of succinylcholine for rapid sequence intubation as prolonged paralysis may result.

Decontamination:

- GIT: Do not perform gastric lavage as it could constitute substantial risk of aspiration in patients with increased secretions and decreased mental status, and this intervention has never been shown to decrease morbidity or mortality.

- Forced emesis is contraindicated because of the risk of aspiration and seizures.
- Activated charcoal (AC) may be given to patients presenting within one hour. The standard dose is 1 gm/kg (maximum dose 50 gm).
- Skin and scalp: careful brushing by soap and water. Hair cutting are essential for successful decontamination (if exposed).

Antidotes:

- Atropine: is used to treat muscarinic effects (e.g. salivation, lacrimation, defecation, urination, bronchorrhea). Dose: Adults: 1-3 mg IV; children: 0.02 mg/kg IV. Three to five minutes after giving atropine, check the pulse, blood pressure, pupil size, sweating and chest sounds. If no response, double the dose and continue doubling the dose q 3-5 minutes when the response is still absent. Once the parameters have begun to improve, cease dose doubling. Similar or smaller dose can be used as required to dry pulmonary secretions. Once secretions are dried, maintain with an infusion of 10% - 20% of the loading dose every hour.
- Oximes: Oxime therapy should be given to all patients with evidence of cholinergic toxicity, patients with neuromuscular dysfunction, or patients with exposures to organophosphates agents known to cause delayed neurotoxicity.
- Pralidoxime Dose: Adult loading dose 1-2 gm IV (or 30 mg/kg) over 20 min followed by an infusion of 500-1000 mg/hr (or 8 mg/kg/hr). Children loading dose 25-50 mg/kg (2 gm maximum) followed by infusion of 10-20 mg/kg/hr.
- Obidoxme (toxogonin): For adults give 1 Amp (250mg) over 15-30 min IV as a loading dose then 30 mg/hr.
- Oximes should be continued 24 hrs after the patient is free of cholinergic manifestations.

- N.B. Evidence about the use of oximes to treat OP poisoning is difficult to interpret. Pralidoxime is not generally recommended in cases of known exposure to carbaryl (Sevin) due to exacerbation of toxicity in animal models, although its use/nonuse in such situations is still a matter of controversy. Until this variability is better confirmed and other treatments become available, we believe that all organo-phosphorus poisoned patients should be treated with oxime.

Supportive treatment:

- Seizures: Organophosphate induced seizures should be treated with a benzodiazepine (diazepam 5-10 mg IV, lorazepam 2-4 mg IV; repeat as needed).
- Management of ventricular arrhythmias (torsades de pointes): by Mg sulphate and atropine, correct hypokalemia and bradycardia. Avoid class III antiarrhythmics.

COMMON PITFALLS

- Inadequate initial atropinization. Patients with severe toxicity require rapid administration of large doses. Titrate to the endpoint or drying pulmonary secretions.
- Monitor respiratory function closely, pulmonary function testing may provide early clues to the development of respiratory failure.
- Some component of dermal exposure occurs with most significant exposures, inadequate decontamination may worsen toxicity.
- Patients should be monitored closely for 48 hrs after discontinuation of atropine and pralidoxime for evidence of recurrent toxicity or intermediate syndrome.

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PYRETHRINS AND PYRETHROIDS

INTRODUCTION:

Description:

- Pyrethrins compounds are naturally presenting insecticides extracted from the chrysanthemum plant. Pyrethroids are totally synthetically developed components similar to pyrethrin. Acute human toxicity from exposure to these insecticides is not common; although, they can produce dermal and upper respiratory tract irritation and hypersensitivity anaphylactic reactions. Common pyrethrin-containing pediculicides component involve A-200, Triple X, and RID.

Forms and uses:

- **Naturally occurring components (pyrethrins)** involve Pyrethrin I, Pyrethrin II, Jasmolin I, Jasmolin II, Cinerin I, and Cinerin II.
- **Synthetic components (pyrethroids**) involve Barthrin, Phenothrin, Cyfluthrin, Flucythrinate, Fenproponate, Fenproparthrin, Tralomethrin, and Tralocythrin
- Pyrethrin and pyrethroid insecticides components are specified by their very rapid "knock down" insect poisoning act.

Toxic dose:

- Allergic pyrethrins/pyrethroids reactions in susceptible exposed case may occur at any dose.
- Even large ingestions rarely depvelp toxicity.
- Oral toxic dose is estimated as more than 100 - 1,000 mg/kg.
- The lethal acute oral pyrethrins/pyrethroids dose is 10-100 g.

Pathophysiology:

- In insects, pyrethrins and pyrethroids component are rapidly develop death by paralyzing the nervous system through disturbances of the membrane ion transport system in nerve axons, and pyrethroids prolong sodium ion influx and also may block inhibitory neurotransmitter pathways.
- In mammals, they are generally able to metabolize these pyrethrins and pyrethroids compounds rapidly and thereby produce them harmless compounds.

Epidemiology:

- Pyrethrins/pyrethroids exposure is common, but toxicity is rare.
- Poisoning manifestations following exposure are typically mild degree.
- Pediatrics are considered more sensitive to pyrethrin compound toxic exposure due to their inability to hydrolyze pyrethrin esters effectively.
- Death may develop after a massive amount of ingestion.

Causes:

- Pyrethrins/pyrethroids toxicity usually develop via inhalation route of exposure.
- Accidental orally route ingestions also have been reported in Saudi Arabia.

Risk Factors:

- Jobs at risk for exposure are farmers.
- Cases with allergy are at high risk for pyrethrins/pyrethroids toxicity

CLINICAL MANIFESTAIONS

- Pyrethrins/pyrethroids poisoning to humans is composed primarily with hypersensitivity reactions and direct irritant effects.
- **Anaphylactic manifestations:** Anaphylactic reactions involving bronchospasm, oropharyngeal edema, and anaphylactic shock may develop in hypersensitive cases.
- **Respiratory manifestations:** Inhalation of pyrethrins/pyrethroids compounds may develop wheezing in persons with asthma.
- **Dermal manifestations:** Dermal exposure may develop burning, tingling, numbness, and erythema.
- **Ocular manifestations:** Accidental ocular exposure during scalp application of pediculicides component has caused corneal damage, invoving keratitis and denudation.
- **GIT manifestations:** With large ingestions (200-500 mL of high concentrated pyrethrins/pyrethroids solution), the CNS may be suffered, resulting in seizures, coma, or even respiratory arrest.

INVESTIGATIONS

General Tests:

- Electrolytes levels, random blood glucose, and arterial blood gases or oximetry are useful and helpful laboratory investigations

Specific Tests:

- Pyrethrins/pyrethroids compounds are metabolized rapidly inside the

body, and methods for detecting the parent compound are not routinely available in basic health care service.

TREATMENT

Emergency and supportive procedures:

- Manage bronchospasm and anaphylaxis if they develop "General toxicology section"
- Observe cases with a history of large pyrethrins/pyrethroids ingestions for at least 6 hours for any manifestation of neurological depression or seizures.

Specific medications and antidotes therapy:

- There is no specific antidote for pyrethrins/pyrethroids compounds.

Decontamination procedures:

- **Inhalation exposure.** Remove cases from exposure site and give supplemental oxygen 100% if required.
- **Dermal exposure.** Wash with copious amount of water and soap. Topical dermal application of vitamin E in vegetable oil was recorded to relieve paresthesitic sensation effect of pyrethrins/pyrethroids compounds.
- **Ocular exposure**. Irrigate with copious amount of water. After irrigation procedure, perform a fluorescein ophthalmic examination and refer the case to an ophthalmologist if there is sign of corneal damage.
- **Oral exposure**. In the majority of patients, a nontoxic dose has been ingested and no decontamination procedure is necessary. However, after a large ingestion of a concentrated pyrethrins/pyrethroids solution, administer activated charcoal orally if conditions are appropriate. Gastric lavage is not necessary after small to moderate ingestions if activated charcoal can be given promptly.

Enhanced elimination techniques:

- Pyrethrins/pyrethroids are metabolized rapidly by the body, and enhanced elimination procedures would not be expected to enhance their elimination.

FOLLOW UP

Patient monitoring

- Pulmonary monitoring should be performed in symptomatic cases.
- Close continuous cardiopulmonary monitoring should be applied in

severe conditions.

Expected course and prognosis

- Respiratory manifestation occur shortly pyrethrins/pyrethroids exposure, peak within an hour, and completely recover over hours to days with treatment from the onset of toxic exposure.
- Dermal manifestations may take days to weeks for complete recovery.
- Long-term pulmonary or dermal allergic hypersensitivity reactions may be a consequence.
- Chronic exposure to pyrethrins/pyrethroids component may develop reactive airway condition.
- Occupational form of asthma from pyrethrin compound has been recorded in farmers.
- Complications of hypoxia or hypotension may occur in occult, life-threatening conditions.

Discharge criteria/instructions

- **From the emergency department or hospital**
  - Asymptomatic cases may be discharged following decontamination procedures, 4-6 hours of close observation

PITFALLS

- **Diagnosis:**
  - The probability of coingestants with pyrethrins/pyrethroids exposure should be considered, such as hydrocarbons and anti-choline esterase (OP/ON) insecticides exposures.
  - It is critical to closely observe the case for 6 hours for the development of delayed anaphylactic pulmonary manifestations.
- **Treatment:**
  - It should not be considered that pesticide exposure with respiratory manifestation is caused by an organophosphate or carbamate only.
- **Follow Up:**
  - It is important to order for a follow-up outpatient clinic visit with an allergy specialist for all cases with severe allergic manifestations.
  - Delayed anaphylactic hypersensitivity to an acute pyrethrins/pyrethroids exposure may occur, and cases should be instructed to avoid future recurrent exposures from the same situations.

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WARFARIN AND RELATED RODENTICIDES

INTRODUCTION:

Description:

- Dicumarol and other natural anticoagulants compounds are present in sweet clover. Coumarin derivatives are used both therapeutically and as rodenticides preparations. Warfarin (Coumadin) is used widely as a therapeutic anticoagulant drug but is no longer popular as a rodenticide compound because rodents have become resistant to its action.
- The most common anticoagulant rodenticides available currently contain long-acting "superwarfarins" such as brodifacoum, diphacinone, and valone, which have more powerful and prolonged anticoagulant actions.

Forms and uses:

- Coumadin is medically used in the prophylaxis and treatment of venous thrombosis, and pulmonary embolism.

Toxic dose:

- The toxic dose of warfarin and related rodenticides is extremely variable.
- **Warfarin toxic dose:** Generally, a single small ingestion of warfarin (eg, 10-20 mg) will not produce serious toxic manifestations (most rodenticides warfarin preparations contain 0.05% warfarin). On the opposite side, chronic or repeated ingestion of even small amounts (eg, 2 mg/d) can lead to significant anticoagulant toxic manifestation. Patients with hepatic impairment, malnutrition, or a bleeding disorders are at high risk of anticoagulant toxicity. So, a single ingestion does not result anticoagulation unless a massive amount warfarin is ingested.
- **Superwarfarins toxic dose:** Superwarfarins compounds are extremely potent and can have prolonged toxic actions even after a single small superwarfarins compounds ingestion.

Pathophysiology:

- Warfarin produces vitamin K deficiency by stopping the regeneration cycle of active vitamin K and thereby the activation of vitamin K dependent clotting factors II, VII, IX, and X.
- Anticoagulation manifestations is postponed until coagulation factors are depleted.

- Due to its relatively short half-life, a single ingestion of warfarin cannot inhibit synthesis of clotting factors long enough to produce anticoagulation

Epidemiology:

- Warfarin and related rodenticides toxic exposure is common in Saudi Arabia.
- Poisonous manifestations following exposure are typically mild to moderate.
- Death develop in chronic ingestion of warfarin leading to bleeding disorders.

Causes:

- Toxic warfarin and related rodenticides ingestion is usually accidental, by a child

Drug interactions:

- Medications potentiate anticoagulant effect of warfarin include: allopurinol, anabolic steroids, cephalosporin, cimetidine, antidepressants, erythromycin, ethanol, NSAI drugs, sulfonylureas, thyroxin, and many others drugs.
- Warfarin and related rodenticides may develop bleeding at lower levels in cases with preexisting coagulation diorders.

CLINICAL MANIFESTAIONS

- **Excessive anticoagulating disorders** may produce ecchymoses, subconjunctival hemorrhage, bleeding gums, or internal bleeding (eg, hematemesis, melena, hematochezia, menorrhagia, or hematuria). The most immediately life-threatening sequalae are massive GI bleeding and intracranial hemorrhage.
- **The onset of anticoagulant manifestations** from warfarin may be apparent within 15 hours, but with superwarfarins preparations, peak manifestations commonly are postponed for up to 2 days after exposure.
- **Persistent anticoagulant effects** from warfarin may persist for 5 days, whereas anticoagulation from superwarfarins compounds may persist for several weeks, or even months.

INESTIGATIONS

General Tests:

- INR or PT should be detected 12 to 24 hours postingestion to evaluate coagulation effect; if normal, no further evaluation is needed for cases

with warfarin ingestion and a normal PT/INR 48 hours after exposure rules out significant related rodenticides preparations ingestion.

- Partial thromboplastin time, fibrinogen, fibrin degradation products, complete blood count, platelets, stool test for blood, and blood type and cross match should be performed in cases with clinically significant prolongation of INR/PT or reported bleeding.
- Endoscopy may be helpful if clinical evidence of gastrointestinal bleeding is record.

Specific Tests:

- Serum levels of warfarin are not clinically helpful for medical staff.

TREATMENT

Emergency and supportive procedures.

- If significant bleeding develop, be ready to manage shock with transfusions of whole blood and fresh frozen plasma (FFP) and perform immediate neurosurgical consultation if intracranial hemorrhage is suspected.
- Avoid to precipitate hemorrhage in severely anti-coagulated intoxicated cases; prevent falls and other trauma.
- Avoid medications that may accelerate bleeding tendency or decrease metabolic process rate of the anticoagulant.

Antidotes therapy.

Oral Vitamin K1

Indication: Marked prolongation of PT or INR without bleeding.

- **Method of administration.** Vitamin K1 should be given orally. Adult dose is 50-100 mg/day initially in single or divided doses. Pediatric dose is 0.6 mg/kg/day initially in single or divided doses. INR or PT should be repeated measurement daily, and dose increased as needed to normalize INR or PT. Dosage may increase more than 200 mg/day in severe cases
- **Caution.** Complete reversal may not be desired in cases with medical indication for therapeutic anticoagulation.

Parental Vitamin K1

- **Indication. Severe prolongation of PT or INR and frank bleeding**

  (The patient should first receive fresh frozen plasma as described below in symptomatic treatment lines).

- **Method of administration.** Vitamin K1 should be administered

intravenously. Vitamin K1 (25-50 mg) should be diluted with D5W or 0.9% saline and infused slowly at a rate not to exceed 1 mg/min. Dose is not well established in children; initial dose of 0.6 mg/kg or 5-10 mg, titrated to response, is a reasonable reported starting dose. Dose should be repeated two to four times daily; clinician should be prepared to treat any development if anaphylactoid reactions. Parenteral vitamin K1 in doses as high as 400 mg per day have been prescribed.

- **Adverse effects and precautions.** Anaphylactoid reactions and even death have occurred during intravenous use of vitamin K1. In a patient who is anticoagulated for prosthetic valve, vitamin K1 should not be given unless anticoagulation is life-threatening
- No other form of vitamin K should be used (e.g., K2, K3, menadione, K4, or menadiol).

Decontamination procedures.

- Administer activated charcoal orally if cases are appropriate.
- Gastric lavage is not necessary after small to moderate ingestions if activated charcoal can be given promptly and should be avoided in a case with prior anticoagulation.

Enhanced elimination.

- There is no role for enhanced elimination procedures in cases warfarin and related rodenticides.

Symptomatic treatment.

Marked coagulopathy and active bleeding disorders

- Fresh-frozen plasma should be given intravenously; the pediatric dose is 15 - 25 ml/kg, and the adult dose is 2 - 4 units
- On the basis of serial INR and PT measurments, further fresh-frozen plasma may be indicated.
- Bleeding with anemia. Packed red blood cells should be given as indicated.

FOLLOW UP

Patient monitoring

- Serial INR or PT close monitoring is performed to guide treatment of cases with coagulopathy.

Expected course and prognosis

- Complications of hypotension from hemorrhage or intracranial

haemorhage develop rarely.

- If vitamin K treatment is applied before bleeding complications cause injury, a complete recovery is expected.

Discharge criteria/instructions

- **From the emergency department;** Asymptomatic cases with acute single warfarin or related compounds ingestion that is not massive may be discharged after gastrointestinal decontamination procedures and psychiatric evaluation, if indicated.
- **From the hospital;** Cases may be discharged when hemodynamically stable without active bleeding and when INR or PT is normalizing.

PITFALLS

DIAGNOSIS

- Measuring PT/INR too soon following ingestion may result in a pseudo sense of security. At least 12-24 hours should elapse before detection INR or PT.

TREATMENT

- Large doses of vitamin K may be indicated; under treatment is common.
- Severe warfarin overdose in cases requiring therapeutic anticoagulation, e.g., patients with prosthetic heart valves, may require slow partial reversal of anticoagulation; PT should be monitored several times daily to assist in detecting quantity and times of fresh-frozen plasma treatment line.

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CARBON MONOXIDE

INTRODUCTION:

Description:

- Carbon monoxide Gas (CO) is a colorless, odorless, tasteless, and nonirritating gas “Silent Killer” resulted from the incomplete combustion of any carbon-containing compound.

Forms and sources:

- Common sources of human CO exposure routes involve accidental smoke inhalation in fires; automobile exhaust fumes in a closed space; usage of kerosene, or gas stoves; and, to a lesser extent, cigarette smoke “both active and passive smoking”. CO toxicity accounts for frequent emergency department visits every year in the Saudi Arabia.

Toxic dose:

- Most sources of CO gas can give adequate loads to rapidly develop life-threatening poisoning.
- Heavy cigarette smoking can give a carboxyhemoglobin level of up to 12% in active cigarette smokers.
- The recommended workplace limit level for CO gas is 25 ppm as an 8-hours time-weighted average. The CO gas level considered immediately dangerous to life is 1200 ppm (0.12%). However, the duration of exposure to CO gas is very critical. Whereas exposure to 1000 ppm (0.1%) eventually will develop in 50% saturation of CO-Hgb, it may take several hours to reach that level.
- Short exposure to much higher CO levels may give a more rapid increase in CO-Hgb.

Pathophysiology:

- CO poisoning is a sequelae of tissue hypoxia.
- CO binds to hemoglobin structure with an affinity 250 folds that of oxygen, leading to reduced oxyhemoglobin saturation degree and declined blood oxygen-carrying capacity power.
- The oxyhemoglobin dissociation curve is shifted to the left side, decreasing oxygen delivery at the peripheral tissues.
- CO gas directly inhibits cytochrome oxidase enzyme, more disturbance cellular function, and it binds to myoglobin, leading to impaired myocardial contractility power.

- Fetal hemoglobin is highly sensitive to binding by CO gas, and fetal carboxy-haemoglobin levels may be higher than maternal carboxy-hemoglobin concentrations..

Epidemiology:

- Carbon monoxide gas toxicity is one a leading cause of fatal toxicity world wide.
- Posoning CO effects following exposure are typically related to the dose of CO gas (CO concentration × CO duration of exposure).
- CO death is common, and usually develops before the patient reaches a health-care providing site.

Causes:

- The cause often be accidental.

Risk Factors:

- Working in proximity to an internal combustion device source such as a furnace or automobile engine rise the risk of carbon monoxide gas toxicity.
- Infants and children may be at higher risk of CO poisoning because their CO exposure is raised by high minute respiratory intoxicated air ventilation volume and high pediatric metabolic rate.
- Elderly cases are more susceptible to CO toxicity and may have a high incidence of long-term hypoxic CO consequences.
- Carbon monoxide gas poisoning may have teratogenic and embryotoxic possible effects when the CO exposure has been sufficient to cause CO maternal poisoning.
- CO exposure during pregnancy may lead to fetal neurological damage, fetal death, and high incidence of spontaneous abortion.

CLINICAL MANIFESTAIONS

- Manifestations of CO toxicity are mainly in organs with high oxygen demands, such as the brain and heart.
- The majority of cases manifest headache, dizziness, nausea, vomiting and abdominal pain. Cases with ischemic heart disease may represent with angina or myocardial infarction. With more severe CO exposures, sluggish thinking, syncopal attacks, marked disturbed consciousness level up to coma, convulsions, cardiac arrhythmias, hypotension, and death may develop.

- Carboxyhemoglobin concentrations do not correlate with the severity of CO poisoning, however, a CO concentration above 25% is considered significant, and concentrations more than 50% are often associated with severe poisoning.
- Recovered patients from severe toxicity may suffer from multiple neurologic consequences due to a hypoxic-ischemic CO effect, such as parkinsonism, disturbed personality and memory deficits. Some of previous mentions sequelae may have a delayed onset of appearance from several hours to days after CO exposure. Their incidence, may be as high as 50%.
- CO poisoning during pregnancy may develop in fetal demise.

INESTIGATIONS

General Tests:

- Serum electrolytes, BUN, and creatinine are detected to measure anion gap metabolic acidosis or renal impairment effect.
- ECG and cardiac enzymes levels in CO symptomatic cases are ordered to measure possibility of myocardial ischemic CO effect.
- Serial mental status assessments and neuropsychiatric investigations may be required under certain CO poisoning conditions.

Specific Tests:

- Carboxyhemoglobin level from venous or arterial blood is determined to prove CO exposure.
- CO concentrations do not correlate well with poisoning severity degree, except at low CO concentration.

TREATMENT

Emergency and supportive care procedures:

- Keep an open airway and assist ventilation if needed.
  If possibility of smoke inhalation has also reported, advice early intubation for airway protection act.
- Manage coma and seizures if they develop.
- Close continuously monitor the ECG for several hours after CO exposure.
- Because smoke often contains other toxic gases, put the possibility of cyanide toxicity, methemoglobinemia occurrence, and irritant gas damage.

Specific medications and antidotes management.

100% Oxygen:

- Give oxygen in the highest possible oxygen concentration (100%). Breathing 100% warm humid oxygen accelerates the release of CO from hemoglobin to approximately one hour, compared with about six hours in room air normal respiration.
- Use a small tight-fitting oxygen mask and very high-flow oxygen with a reservoir (nonrebreather type) or give the oxygen supply by endotracheal tube.
- Manage until the CO-Hgb level is below 5%.

Decontamination procedure:

- Remove the case immediately from exposure source and administrate oxygen. Rescuers should wear self-contained breathing apparatus “in a high potentially CO concentrations incidents”

Hyperbaric oxygen therapy:

- Order hyperbaric oxygen in severe CO poisoning patients.
- Hyperbaric oxygen give 100% oxygen under 2-3 atm of pressure and can accelerate elimination of CO (half-life decrease to 20 minutes).
- Hyperbaric oxygen will be useful in cases with severe CO poisoning, especially when there is ready access to a hyperbaric oxygen chamber.
- Indication of hyperbaric oxygen therapy:
  - Coma
  - Carboxyhemoglobin level >25%
  - Age more than 35 years
  - Severe metabolic acidosis conditions
  - Abnormal findings in neurologic assessment (cerebral or cerebellar dysfunction)
  - Abnormal findings in cardiovascular assessment (cardiovascular disturbances)
  - Prolonged exposure to CO gas for more than one day.

FOLLOW UP

Patient monitoring

- Close respiratory and cardiac functions monitoring should be applied continuously in CO symptomatic cases.

Expected course and prognosis

- Most CO cases with mild gas exposure do well with treatment of 100% oxygen by face mask.
- Toxic CO manifestations peak in the first few hours from exposure and often resolve over a few hours after stoppage of CO exposure.
- Cases with severe CO exposure may incompletely recover. CO sequelae may range from difficulty in concentration, personality changes to dramatic persistent vegetative status.
- In some CO cases, initial incomplete recovery is followed by persistent neurological damage or appearance of delayed neuropsychiatric disorders.

Discharge criteria/instructions

- **From the emergency department.** Asymptomatic or minimally CO symptomatic cases (without history of coma) may be discharged after 100% oxygen management, when they become completely asymptomatic.
- **From the hospital.** Cases who face the criteria for hyperbaric oxygen therapy indicator may be discharged after one or two treatments lines, if recovered, and following psychiatric assessment, if required. Follow-up visits should be assigned for further treatment and serial neurological evaluation.

PITFALLS

DIAGNOSIS

- CO toxicity should be considered in all cases with food poisoning like symptoms, flulike manifestations, especially if multiple family members are affected with disturbed consciousness level.

TREATMENT

- It is highly needed to order hyperbaric oxygen therapy for moderately or severely CO poisoned cases.
- It is essential to detect the source of CO exposure to avoid re-exposure.
- A blood sample of carboxyhemoglobin level withdrawn a few hours after end of CO exposure can be misleading sample because CO has been completely eliminated. Therapy must be based here on clinical manifestations only.

FOLLOW-UP

- It is important that the case return if manifestations occur after the recovery from poisoning for re-evaluation of delayed neurologic CO sequlae.

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NATURAL TOXINS AND ENVENOMATION

SNAKE BITE

INTRODUCTION:

- All snake species that are medically significant possess one or more pairs of fangs in the upper jaw. These fangs penetrate the skin of their victims and tranfer venom through a groove or closed channel into the tissues. (See the Snake bite chart for the commonest venomous snakes in Saudi Arabia).
- The potency of the venom and the amount of venom injected vary considerably. Some snake strikes are "dry" bites in which no venom is injected.

MECHANISM OF TOXICITY:

- Snake venoms are complex mixtures of components that produce local "digestive" or cytotoxic insult on tissues, in addition to hemotoxic, neurotoxic, and other systemic effects. The relative predominance of cytotoxic, hemotoxic, and neurotoxic venom components depends on the species of the snake and geographic and seasonal variables.

CLINICAL MANIFESTAIONS:

- The first step is to identify whether the snake is poisonous or not. The easiest way is to diagnose from the bite.
- A venomous snake bite is characterized by
  - The bite usually shows 2 holes (refer to canines injecting venom).
  - Spreading pain, numbness, and oedema.
- While *in non-venomous snake bite:*
  - Bite site shows multiple teeth impressions
  - Absent significant local pain or swelling

I- Vipers (family Viperidae)

- Vipers (family Viperidae) are venomous snakes that include 2 subfamilies, true vipers (Vipernae) and pit vipers (Crotalinae). The most common types present in Saudi Arabia are the Puff Adder (*Bitis arietans),* Palestine Saw-scaled Viper (*Echis coloratus*), Saw-scaled Vipers (*Echis carinatus,* and Horned viper (*Cerastes cerastes)*.
- Viperidae envenomation, mainly hematologic:
  - Local manifestations: (Severe)
    - Severe progressive pain.

- Petechiae, serous oozing from the bite site and formation of blood-filled vesicles.
- Progressively spreading swelling (oedema) and bruising at the bite site (The circumference of the swollen bitten limb should be regularly measured and closely observed every 15 minutes). Oedema extends to cover the whole bitten area.
- Gangrene of the bitten area may occur.

- Systemic manifestations:
  - Non-specific systemic effects: Nausea, vomiting, diarrhea, weakness, light-headedness, diaphoresis, and chills
  - Coagulopathy and bleeding.
  - Rhabdomyolysis with nephrotoxicity.
  - Increased vascular permeability, tachycardia, tachypnea, and hypotension.
  - Neurotoxicity (e.g., oral paresthesia, unusual taste, fasciculations, altered mental status, seizures). Crotalid bites usually do not cause neuromuscular weakness with respiratory depression.
- Russell viper envenomation:
  - Russell viper is unique in that it can produce both hemorrhagic and neurotoxic effects which include:
    - Numbness, tingling, cranial nerve dysfunction e.g. (changes in taste and smell), ptosis and external ophthalmoplegia, paralysis of facial muscles, aphonia, and dysphagia.
    - Flaccid paralysis of skeletal muscles and respiratory paralysis.
    - Loin pain, hematuria, hemoglobinuria, myoglobinuria, oliguria/anuria, hyperkalemia and the condition ends by acute renal failure.

Grading of Pit Viper Envenomation	
Dry Bite	Bite mark without severe pain or swelling, normal vital signs, normal coagulation studies and normal platelet count.
Mild	Local pain and swelling, normal vital signs, normal to mildly abnormal coagulation studies and Platelet count >100,000
Moderate	Local pain and moderate swelling, normal vital signs, abnormal coagulation studies (double PT and PTT) and platelets <100,000
Severe	Shock, altered mental status with or without normal vital signs, abnormal coagulation studies, Thrombocytopenia (platelets <20,000)

II. Elapidae (Includes cobras, kraits) mainly neurotoxic

- The most common types present in Saudi Arabia are Arabian Cobra (*Naja Haje Arabicus,* and Desert Black Snake (*Walterinnesia aegyptia*).
  - Indistinct fang marks.
  - Burning pain (may be absent).
  - Mild to moderate oedema (may be absent) and discoloration.
  - Serosanguinous discharge (may be absent).
  - Paraesthesia around bitten area.
  - Muscular incoordination and weakness in the bitten limb.
- Systemic manifestations:

I. Neurotoxicity:

- Pre paralytic stage: Increased salivation and emesis with or without headache
- Paralytic Stage:
  - Dysarthria and dysphagia.
  - Visual disturbances (ptosis and external ophthalmoplegia).
  - Respiratory distress ends by respiratory failure. Most deaths occur as a result of respiratory arrest within 36 hrs.

II. Cardiotoxicity:

- Cardio toxins affect the cell membranes directly causing myocardial depression, cardiogenic shock, and systolic cardiac arrest.

INVESTIGATIONS:

Routine:

All but trivial pit viper bites require

- Measurement of serum electrolytes, BUN, and creatinine
- ABG and EKG monitoring

Specific:

- A baseline CBC (follow hemoglobin, hematocrit, and platelets), and coagulation profile (i.e., INR, PT, and fibrinogen). Repeat these investigations after each course of antivenom and every 4-6 hrs after initial control has been established.
- Measurement of fibrin degradation products.
- Urine analysis: Color, red cell casts and proteinuria.
- Bite site serial assessment and testing: Outlining the leading margin of the local swelling with a marker every 15-30 min can help clinicians assess the progression of the envenomation locally. Bitten extremity circumference should also be measured upon arrival of the patient and at regular intervals until local progression subsides.

TREATMENT:

Pre-hospital:

- FIRST AID: Directed towards reducing the spread of the venom and expediting the transportation of the patient to an appropriate medical facility.

General principles:

- Keep the patient calm.
- Immobilize the injured part of the body in a functional position using a light bandage.
- Transfer the patient to the closest medical facility as fast as possible.
- Withhold any drugs that may confound clinical assessment or interfere with treatment (e.g., anticoagulants, aspirin, NSAIDs, or β blockers).
- Do not remove the immobilization bandage until the patient has reached the hospital, and a clinical assessment regarding the need for antivenom has occurred

First Aid for Snake Bite (Do it RIGHT)

*R: Reassure the patient that most of snake bites are of nonvenomous species.

*I: Immobilize the limb. **Use bandage or cloth to hold splints not to block blood supply or apply pressure.**

*GH: Get to the hospital immediately.

*T: Tell the doctor of any symptoms that developed on the way to the hospital

Hospital

Stabilization:

- Early care of snake bite victims should focus on supporting patients with life-threatening respiratory depression or shock. If pressure immobilization is in place, then it should not be removed until the initial assessment, stabilization, and if needed, antivenom is provided.
- Shock: Rapidly administer normal saline or blood (depending upon the severity of hemorrhage). If shock is not corrected and the CVP is not low, vasoactive drugs may be indicated.

The anti-snake venom (ASV)

- The most critical decision in the management of a snake bite victim is whether or not to administer the anti-venom.

Rules for administration of ASV

- The risk of developing a hypersensitivity reaction should always be considered. Patients having a positive history of atopy (e.g., severe bronchial asthma and atopic dermatitis) are at a higher risk of severe hypersensitivity reactions and should be given ASV under close monitoring during and after treatment.
- Treatment with the antivenom should be administered as soon as it is indicated. It may reverse systemic complications even after several days. It should be given as long as coagulopathy persists.

Indications for anti-snake venom administration:

Local indications:

- The presence of a progressive local swelling involving more than half of the bitten limb (in the absence of a tourniquet) within 48 hrs of the bite.
- Rapid extension of the swelling within a few hours of the bite on the hands or feet.
- Development of an enlarged tender lymph node draining the bitten area.

Systemic indications:

- Clinical indications:
  - Spontaneous systemic bleeding.
  - Neurotoxic signs: Ptosis, external ophthalmoplegia, paralysis etc.
  - Hypotension, shock, cardiac arrhythmia and /or abnormal EKG.
  - Oliguria and/or anuria.
  - Rhabdomyolysis.
- Laboratory indications:
  - Prolonged PT and thrombocytopenia (<100000).

- Elevated BUN, creatinine and serum K.

Administration of ASV:

Two methods of administration are recommended:

- Intravenous injection: The physician must remain with the patient during time of early reactions (up to 180 minutes).
- Intravenous infusion over one hour.

Anti-Snake Venom Doses:

For pit viper envenomation:

- The main course of treatment is the polyvalent antivenom. The degree of effectiveness of this antivenom is both time and dose dependent. It has the highest effectiveness in preventing venom-induced tissue damage when given early. It is less effective if delayed but can reverse coagulopathies and be effective even when started 24 hrs after envenomation.
- Administer a loading dose of 5 vials of reconstituted polyvalent immune Fab diluted in 250 mL of normal saline slowly at 20-50 mL/hr for the first 10 min.
- If no adverse reactions are noted, the remainder of the doses should be infused over the next hour. The same dose can be repeated twice every 4-6 hrs until improvement is sufficient to achieve the initial control of symptoms, reverse coagulopathies, and correct vital parameters.
- In children, the dose is is the same as in adults. The limb circumference should be measured at 3 points proximal to the bite.
- Additonally, the advancing border of the swelling should be measured every 15-30 min as it can guide decisions about the need for further administration of additional doses.

For the cobra snake envenomation:

- 5 amp of the bivalent antivenom diluted in 250 ml saline, infused IV. More antivenom should be administered if severe signs persist after 1-2 hrs and dose can be repeated every 4-6 hrs until improvement.

N.B. double the dose of the polyvalent antivenom if the bivalent antivenom is not available.

After Administration of ASV, the victim should be observed for:

- General condition.
- Spontaneous systemic bleeding and decreased blood coagulability.
- Neurological or cardiovascular symptoms.

- Urine color due to hematuria.

Criteria for repeating the ASV:

- Uncoagulability after 6 hrs.
- Persistence or recurrence of bleeding after 1-2 hrs.
- Deteriorating neurotoxic or cardiovascular signs after 1-2 hrs.

Supportive treatment:

- Patients should receive tetanus prophylaxis (toxoid). Snakebites do not usually become infected and antibiotics are indicated only for patients with clinical evidence of infection.
- Coagulopathy: Blood products (e.g., whole blood, fresh frozen plasma, or platelets) only if life-threatening bleeding and, when available, after antivenom administration
- Rhabdomyolysis: Antivenom may attenuate but does not reverse rhabdomyolysis after a snakebite. Rhabdomyolysis treated by rapid infusion of isotonic saline.
- Perform proper local wound care after Initial stabilization and complete assessment, and if needed, intravenous antivenom is being provided.

COMMON PITFALLS:

- The following methods, while used widely in the past and advocated by some, cause more harm than good and should be avoided:
  - Incision and oral suction.
  - Mechanical suction devices.
  - Cryotherapy
  - Surgery
  - Electric shock therapy
  - Tourniquets may cut off arterial blood flow and cause significant ischemic damage, especially when left on for a prolonged period of time.

SNAKE BITE OBSERVATION FORM

Patient name: ..... Date & time of bite: .....
Date of birth: ..... Number of bite: .....
ER number: ..... Type of snake: .....

Time After Bite:										
Vital signs:										
Pulse										
Blood pressure										
Temperature										
Local signs:										
Local bite site pain										
Local bite site swelling										
Reg. lymph node tenderness										
General manifestations:										
Headache										
Nausea										
Vomiting										
Abdominal pain										
Hematological signs:										
Persistent blood ooze										
Hematuria										
Active bleeding										
Neurological signs:										
Ptosis										
Ophthalmoplegia										
Fixed dilated pupils										
Dysphagia										
Dysarthria										
Tongue protrusion										
Limp weakness										
Respiratory weakness										
Myolytic signs:										
Muscle pain										
Myoglobinuria										
Renal:										
Urine output										
Laboratory findings:										
PT/INR										

Time After Bite:										
aPTT										
Hemoglobin count										
Platelet count										
Fibrinogen										
FDP										
CK										
BUN										
Creatinine										
K+/Na+										
ABG finding										
Antivenom:										
Type										
Amount										
Time of administration										

Snake Bite

If there are clear fangmarks or the snake was positively identified as poisonous

If no fang marks or the snake was positively identified as non-poisonous

Give antitetanus toxoid and observe for 24 hrs
Are there any noticeable clinical manifestations?

Give antitetanus toxoid and observe 4-8 hrs.
Are there any noticeable clinical manifestations?

No → **Discharge**

Yes → Determine if the snake is hemotoxic or neurotoxic or mixed

Yes → Determine if the snake is hemotoxic or neurotoxic or mixed

No → **Discharge**

Hemotoxic

Expected local and systemic manifestations:
Pain, local swelling, blistering and bruises, spontaneous systemic bleeding.
Laboratoryinvestigations:
CBC, PT, PTT, FDP, Fibrinogen.
Expectedlabresults:
Increase: PT, PTT, FDP. Leukocytes, Hematocrit
Decrease: Hb, Platelets, RBCs, Fibrinogen

Treatment
Snake antivenom:
Polyvalent antivenom after doing sensitivity test
Dose: 5 amp. dilute in 250ml saline and can be repeated every 4-6 hrs until improvement
(Children receive the same dose as adults)
SupportiveTreatment: fresh frozen plasma, platelets concentrate and blood transfusion.

Neurotoxic

Expected manifestations:
Ptosis, external ophthalmoplegia, progressive paralysis of the face, palate, vocal cords, neck muscles and respiratory muscles with progressive respiratory failure.
Laboratoryinvestigations: ABG

Treatment
Snake antivenom:
Bivalent antivenom after performing sensitivity test. Dose: 5 amp diluted in 250 ml saline. More antivenom should be given if severe signs persist after 1-2 hrs and dose can be repeated every 4-6 hrs until improvement (Children receive the same dose as adults) N.B. Double the dose of the polyvalent antivenom if bivalent not available
Supportive Treatment: assist ventilation and mechanical ventilation if in need

Puff Adder
Bitis arietans
الأفعى النفاثة

Palestine Saw-scaled *Echis coloratus* Viper
أفعى السجاد الشرقي

Saw-scaled *Echis carinatus* Vipers
أفعى الطفي منشارية الحراشف

Horned viper
Cerastes cerastes
الأفعى المقرنة (أم جنيب)

Arabian Cobra
Naja Haje Arabicus
الكوبرا العربية

Desert Black Snake
Walterinnesia aegyptia
كوبرا الصحراء الأسود
الصل الأسود

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SCORPION STING

INTRODUCTION:

- Scorpion venoms are complex and the components are species specific. (See the Scorpion chart for the common types present in Saudi Arabia).

MECHANISM OF TOXICITY:

- The scorpion venom contains varying concentrations of various toxins e.g., neurotoxin, cardiotoxin, nephrotoxin, hemolytic toxin, phospho-diesterases, phospholipases, hyaluronidases, glycosaminoglycans, histamine, serotonin, tryptophan, and cytokine releasing toxins.
- Venom toxins alter sodium channels, leading to prolonged neuronal excitability.
- Many end-organ manifestations occur secondary to this excessive excitability. The cardiopulmonary effects observed after some scorpion envenomations occur as a result of autonomic excitability. Neuromuscular overstimulation leads to somatic and cranial nerve hyperactivity.
- Serotonin may be found in the scorpion venom and is thought to contribute to the pain associated with scorpion envenomations.

CLINICAL MANIFESTATIONS:

- Mild envenomation: Local manifestations only including pain, localized paresthesias or burning, very mild local oedema, and localized sweating.
- Moderate envenomation: Local manifestations in addition to systemic manifestations such as sialorrhea, generalized diaphoresis, nausea, vomiting, abdominal pain, mild tachycardia, hypertension, mild tachypnea, restlessness, drowsiness, ataxia and priapism.
- Severe envenomation: May present with severe hypertension or hypotension, pulmonary oedema, myocardial failure.
- EKG may show ST segment or T wave abnormalities, dysrhythmias, respiratory failure, CNS depression, symptomatic pancreatitis or upper GI bleeding.
- Children are at a higher risk than adults to develop severe systemic manifestations, and the majority of mortalities reported are in children below 10 years of age.

INVESTIGATIONS:

Routine:

- Monitor serum glucose and electrolytes, initiate continuous cardiac monitoring and obtain an EKG in patients with moderate or severe manifestations of envenomation.

- Obtain a chest radiograph and monitor pulse oximetry and/or arterial blood gases in patients with respiratory signs or symptoms.

Specific:

- Serum lipase (for patients presenting with abdominal pain or persistent vomiting).
- Follow markers of myocardial injury (troponin, CK-MB or myoglobin) in patients with severe envenomation.

TREATMENT

Asymptomatic or mild envenomation:

- Most scorpion stings result in mild envenomations (Grade I or II).
- Pain management with oral medications (e.g., NSAIDs).
- Clean the sting site, and tetanus prophylaxis is advised.
- These patients should be observed for 4 hrs to ensure that there is no further progression of symptoms. The progression of envenomation grade in children may occur rapidly.
- Prior to discharge, patients should tolerate oral intake, have no progression of symptoms, and their pain should be adequately controlled with oral medications.

Moderate and severe envenomation:

Stabilization:

- ABC, administer oxygen and monitor airway carefully in patients with respiratory signs or symptoms. Excessive secretions and tachypnea are common, and pulmonary oedema may develop with severe envenomation. Endotracheal intubation and ventilation may be necessary in some cases.
- Analgesics may be required for pain control.

Supportive treatment:

- Proper care of respiration, endotracheal intubation in patients with significant difficulties maintaining their airway or with pulmonary edema accompanied by hypoxemia.
- Close monitoring for and treatment of myocardial ischemia and/or acute decompensated heart failure in patients at risk.
- Intravenous fentanyl 1 µg/kg for pain. Fentanyl is preferred if antivenom administration is planned because, unlike morphine, fentanyl does not cause histamine release.
- Intravenous benzodiazepines (lorazepam or continuous midazolam infusion), titrated for sedation and to treat muscle spasticity if antivenom is not used.

Antivenom (polyvalent anti scorpion serum)

- It is the treatment of choice. The dose used is determined by the severity of the clinical manifestations.
  - If the patient is asymptomatic, do not give the antivenom and observe for 6 hrs.
  - If the patient presented after 6 hrs and is asymptomatic do not give anything and discharge.
- If symptomatic, administer an initial dose of 5 amp of the polyvalent anti scorpion diluted in 20 - 50 ml saline given IV over 20 minutes. If the systemic manifestations still exist, the same dose can be repeated q 2 hrs up to 4 doses.
- The antivenom`s main function is to decrease the levels of circulating unbound venom. In some cases, symptoms may still persist inspite of the prompt administration of the antivenom. This is could be attributed to the inability of the antivenom to counteract the toxins that are already bound to their target receptors. Therefore, symptomatic and supportive treatment is needed with immunotherapy.

Summary Scorpion sting evaluation and treatment:

Grade	Clinical findings	Treatment
I	Localized pain or paresthesias at site	Symptomatic care, ie, analgesics, anxiolytics
II	Local and remote pain or paresthesias	Symptomatic care, ie, analgesics, anxiolytics
III	Localized pain with paresthesias and either: Cranial nerve abnormalities or Somatic skeletal neuromuscular dysfunction	Symptomatic care and supportive care, ie, analgesics, anxiolytics; give antivenom if available
IV	Localized pain, cranial nerve abnormalities, somatic skeletal neuromuscular dysfunction, and airway involvement are all present	Symptomatic care and supportive care, ie, analgesics, anxiolytics; give antivenom if available

Scorpion sting

Is the patient presenting with any systemic manifestations or severe local reaction?

Local reaction, burning pain
No systemic signs

- Reassure
- Analgesic orally
- Clean the wound
- Local anesthetic infiltration
- Tetanus prophylaxis
- Observe for 4-8 hrs for appearance of any systemic manifestations?

No

Discharge

Leiurus quinquestriatus

Androctonus crassicauda

Assess: Severe local inflammatory reaction, severe pain, vomiting, priapism, fever, hypo or hypertension, tachycardia, arrhythmia, shock, respiratory distress, pulmonary edema, tremors, agitation, CNS depression, parasthesia, muscle fasciculations, cranial nerve palsy, muscle weakness, paralysis, nystagmus and seizures

Yes

Admit to ICU
Establish airway, breathing, and circulation (ABCs)
Monitor: Vital signs, EKG, coagulation profile, RBS, ABG, CBC, LFTs, RFTs, O_2, IV Fluids, CVP, amylase/lipase, creatine kinase and urinalysis

Treatment

Scorpion antivenom: ***(After performing a sensitivity test)***

- It is best given in the first 4 hrs but can still be given as late as 24 hours.
- *Dose:* 5 amp polyvalent antiscorpion diluted in 20 - 50 ml saline given IV over 20 minutes. If systemic manifestations still exist the same dose can be repeated q 2 hrs up to 4 doses. *Observe* for any adverse effects of the antivenom.

Supportive Treatment:

Asymptomatic or mild envenomation:

1. Most scorpion stings result in mild envenomations (Grade I or II).
2. Pain management with oral medications (e.g., NSAIDs)
3. Clean the sting site and tetanus prophylaxis suggested.

Severe envenomation:

4. Proper care of respiration, endotracheal intubation if needed
5. Close monitoring for and treatment of pulmonary edema.
6. Close monitoring for and treatment of myocardial ischemia and/or acute decompensated heart failure in patients at risk.
7. IV fentanyl 1 µg/kg for pain.
8. IV benzodiazepines for sedation and to treat muscle spasticity
9. *Atropine* to control venom-induced parasympathomimetic effects.
10. Keep the patient under observation for at least 24 hrs after recovery

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NON-TOXIC INGESTION:

INTRODUCTION:

Description:

- A case presentation that represents an exposure to a compound thought to be nontoxic.
- A substance should be considered nontoxic category only if the following conditions are met:
  - The product has been completely identified.
  - Only one compound is involved in the incident.
  - The covered label does not contain any warning from the Consumer Product Safety Manufacture, and the substance in the bottle appears to be the original product (i.e., no replacement has occurred).
  - The amount of substance ingested can be accurately calculated.
  - The route of substance exposure can be accurately detected.
  - The case is completely free of signs or symptoms of substances effect, both at subjectively and objectively levels.
  - Follow-up procedure must be both easily available and highly reliable (e.g., parent or guardian).
  - If any of these previous mentioned conditions are not met or are questionable, the case should be managed as an unknown ingestion condition. As Paracelsus stated, "All substances are poisons; there is none that is not a poison, the right dose differentiates a poison and a remedy."

Pathophysiology:

- By definition, a nontoxic ingestion should not develop any adverse toxic health effects. Massive ingestions may produce some mild effects such as GI upset or irritate/obstruct the airway passage.

Drug interactions:

- Non-toxic substances may interact with drugs that are being taken for therapeutic purposes.

DIAGNOSIS

Differential Diagnosis

- Following is an alphabetical list of items generally considered to be nontoxic.

Household Items	
Ashes	Deodorant
Baby Products	Erasers
Ballpoint Pen Ink	Fabric Softener
Body Conditioner	Felt-Tip Pens
Bubble Bath	Hand Lotions
Candles	Highlighting Markers
Caps For Toy Guns	Indelible Markers
Caulk “Accredit Source”	Kitty Litter
Charcoal	Latex Paint
Clay	Laundry Detergent (Liquid)
Cosmetics	Lipstick
Crayons “Accredit Source”	Magic Markers

Household Items

Newspapers Produced In The US
Pencil Lead (Actually Graphite)
Petroleum Jelly
Pet Foods Or Chew Toys *(Not Including Pet Medications)*
Photographs
Plastics
Playing Cards
Play-Doh
Rubber Cement
Shaving Cream
Shampoos
Silica Gel
Soaps
Spackle
Starch
Sunscreens
Sweeteners
Teething Ring Contents
Toothpaste
White Glue

Plant

Many categories of plants are nontoxic. Due to regional variations in names of plants, a regional poison control center should be contacted if a substantial amount of any plant is ingested. A partial list of nontoxic plants is as follows:

African Violet
Aralia
Baby Tears
Bird's Nest Fern
Bridal Veil
Coleus X Hydrus
Corn Plant
Creeping Jenny
Dracaena Indivisa
Dwarf Schefflera
Emerald Ripple
Fiddle-Leaf Fig
Gardenia
Grape Ivy
Jade Plant
Wandering Jew
Parlor Palm
Peacock Plant
Piggyback Begonia
Piggyback Plant
Prayer Plant
Rubber Tree
Snake Plant
Spider Plant
String Of Hearts
Swedish Ivy
Velvet Plant
Wax Plant
Zebra Plant
Wandering Jew

Medications

Antacids
Calamine Lotion
Birth Control Pills (If Single Ingestion)
Corticosteroids (If Single Ingestion)
Mineral Oil (Unless Aspirated)
Oral Antibiotics (Some Exceptions)
Water-Soluble Vitamins (Excluding Iron)
Zinc Oxide
Zirconium Oxide

Signs and Symptoms

- History taking is a main factor in detecting a nontoxic ingestion.
  - What substances did the case have access to?
  - What drugs were prescribed to the case or other family members?
  - When was the last time the case was seen Normally?
  - Were there initial manifestations that have recovered?
  - Were substances at the scene of incident brought to the ER for possible toxicological identification and/or analysis?
- There should be **no signs or symptoms at the time of presentation**.
- If they do manifestations occur, the case should be managed as an unknown ingestion.

Laboratory Tests

- If taken history confirms a nontoxic exposure condition, no non-toxicological or toxicological testing is required. Suicidal attempts should be treated as unknown ingestions, even if the case claims that only nontoxic substances were ingested.

TREATMENT

Directing Patient Course

- Dosage and timing should be determined for all compounds that could be involved. It is important to evaluate the need for toxicological consultation with a regional poison control center or other concerned specialists in order to confirm the lack of toxicity of the suspected ingestion.

Decontamination

- Do not produce any decontamination procedures for a full-ensured diagnosed nontoxic ingestion.

PITFALLS

- Failure to accurately detecting compound(s) ingested and confirm their lack of toxicity “non-toxic category”.

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ROLE OF TOXICOLOGY LABORATORY:

I- Basics:

Description:

- A drug screen tests for a large spectrum of substances. It may be tested on urine or blood, depending on the particulated drugs and procedures that are used. Unfortunately, the drugs detected by a drug screen vary among clinics.
- The drug screen is a close to the history and medical examination in the evaluation of the intoxicated patient. It rarely gives critical information but may be helpful to evaluate patients in whom clinical data fails to give an accurate diagnosis.

Forms:

Urine Drug Screening

- Urine is the specimen of choice for drug screens because most drugs and their metabolites are excreted in a concentrated forum in the urine.
- The two major procedures used in drug screens are immunoassay and chromatography. Mass spectrometry can be utilized in combination with chromatography to confirm drug detection more accurately.

- **Immunoassay**
  - A drug-specific antibody conjugate to the target substance. The antibody-drug complex produced is then identified by one of several procedures (enzymatic immunoassay reaction, fluorescence immunoassay, or radioisotope immunoassay labeling).
  - The advantages of choosing this procedure involve fast turnaround and the requirement for minimal sample preparation and handling. This release time and costs approximately low.
  - This is the procedure utilized in most laboratories. However, multiple bedside techniques also use this procedure (e.g., Triage and Verdict).
- **T.L.Chromatography:**
  - The various solubility of substances in polar and nonpolar compartment is used to separate the different substances in a specimen. The most common procedure is thin-layer chromatography (Toxilab), although liquid or gas chromatography columns are indicated as well, depending on the substances to be detected.
  - After separation, the substances are then detected by color appearance.
  - Chromatography can identify a large spectrum of drugs but has multiple disadvantages. The procedure contains substantial sample preparation, and interpretation needs experienced technicians. In

addition, cross-reactivity among substances may locate, thus giving only probable detection of substances in the urine sample.

- **Mass Spectrometry**
  - Mass spectrometry (MS) is conjugated with gas chromatography (GC/MS) and is utilized to assure the substances detected by other procedures.
  - The substances molecular structure is bombarded, dividing it into multiple fragments. These parts are then detected by comparison with a computer database of parts of known substances.
  - The advantage of this procedure is high accuracy in detection. However, this procedure is relatively time consuming and high cost and need well-trained technicians.

Serum Drug Screening

- For some drugs (acetaminophen, anticonvulsants, salicylate, theophylline, ethyl alcohol, ethylene glycol, isopropyl alcohol, lithium, methanol), screening is best produced on a serum specimen.

Indications

- There are no absolute indications for drug screens. Routine urine toxicology screening in overdose cases is high-cost and should be stopped.

Recommended Uses of Drug Screening:

- The patient has a disturbed conscious level of undetected cause. Drug detecting in this scenario may give data and confirm the cause of disturbed conscious level.
- Reported suspected ingested substances do not correlated to medical manifestations. For example, if a case has reportedly exposed a benzodiazepine medication, but has a heart rate of 130 beats/min, further investigation must involve a drug screen to evaluate for the presence of stimulants substances, tricyclic antidepressants medication, or other drugs.
- Athletics. Substance screening is performed in athletics to discover illegal procedure of enhancing performance.
- Brain Death. Diagnosis of brain death should not be identified until the presence of CNS depressant substances has been excluded.
- Intoxication. Substances screens may be helpful if intentional toxicity is suspected.
- Pregnancy. If substance abuse is suspected, substance testing of pregnant female at the time of delivery may direct the way for a social service act.
- Psychiatric. Substance screening in cases with psychiatric symptoms may indicate a toxic etiology.

- Treatment Programs. Substance screens may be helpful if noncompliance with drug treatment protocol is suspected.
- Workplace. Substance screening in the workplace is utilized to identify high-risk potential employees and to decrease risk of occupational accidents.

Method of Use

Preparation

- It should be detected how long it will take for investigated test results to return. In order to have a meaningful effect on immediate patient medical intervention, test results should be released within one hour.
- Substance screens should be indicated only after the treating medical staff has detected what actions will be performed when the results are appeared. For example, serum drug levels of unusual substances are rarely of medical value because the correlation of serum level to poisoning or prognosis is undetectable. Furthermore, these investigative results may not be ready for several days.
- Contacting a clinical toxicologist for advice relating the usefulness of substance screening should be involved.
- Prior to collecting the samples, consider contacting the laboratory technician to assure that the samples is rightly collected and stored.

Collection

Urine

- Sample Collection. A urine specimen of 20-100 cc should be collected and sent to the laboratory. Be aware to procedure used to adulterate the presence of drugs in urine sample. Ambulatory patients giving a specimen for analysis should be observed to avoid adulterating or replacement of another specimen.
- Specimen Handling. The specific substance being suspected or the clinical case scenario should be contacted to the laboratory. This shall allow the technician to better comment the obtained results or to provide the physician that the specimen may not be discovered by the procedures that are available at the laboratory.

Blood

- Sample Collection. Before to collecting the sample, consider contacting the laboratory technician to confirm that the sutiable type of collecting tube is utilized.
- Sample Handling. The specific substance being suspected or the medical situation should be contacted to the laboratory. This will allow the laboratory technician to better comment the results or

to support the physician that the specimen may not be identified by the procedures that are present.

II- Pitfalls

Diagnosis

- Negative" substance screen. The inability to detect a substance does not equal that it is not situate.
  - The substances of interest may not be involved on the panel used.
  - The urine sample concentration may be too dilute for detection of the target substance.
  - The urine sample may have been obtained before the substance was excreted.
  - The specimen may have been adulterated with (rare in the acute disease situation but common in work-related substance screening).
  - Detection of a substance in urine does not provide data about the clinical manifestations of the substance. Most substances assays will detect substances days after the clinical manifestations are relieved.

Immunoassay

- Immunoassays are limited to detection of the specific substances involved in the assay spectrum. Other substances with same effects may not be identified (e.g., opiate immunoassay kit screens panel do not identify methadone or fentanyl).
- Immunoassay procedure also may cross-react with substances that are molecular structurally similar but produce other clinical manifestations. If a substance test is recorded as positive for an illegal substance, it is critical that the test result is confirmed by GC/MS for medico-legal indications.

Thin-layer chromatography

- Thin-layer chromatography obtained results are technician dependent, and a large spectrum of tests are required to maintain proficiency.

Drug screen

- Some substances are not identified by most substance screens. These include iron, cyanide, hydrocarbons, lithium, heavy metals, toxic alcohols, LSD, and many rare drugs.

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Substances of Abuse Testing "Specimen Collection"

Overview:

- Toxicology Laboratory provides suggested sample collection guidelines ONLY. It is the responsibility of individual collection institute to adapt their own policies and procedures according to their requirement in accordance with internal authority rules. Laboratory drug and alcohol test results are usually used in legal issues. The pattern in which samples are collected and handled is very critical. Samples must be handled and controlled by collection site personnel throughout the collecting cycle. A uniform urine and oral fluid obtaining procedure, regardless of the investigating environment, must be applied.

Site preparations:

Principle:

- Requirements for sample collection vary according to the need for which the results will be utilized. However, to reach accepted requirements the sample collection site should be secure in order to exclude the possibility of sample adulteration or replacement and to assure the security of the collected sample.

Collection Area Guidelines:

- **S**ecure & Clean Collection Area
  - Collection site equipment is secure, well lit, and clear of any sites where adulterants materials or replaced sample can be hidden. Furthermore; a clear clean working surface for the collecting technician to utilize as a sample manipulated area.
- **S**ecure Collection Supplies Source:
  - Storage site for collection equipment and related articles is secure.
- **S**ecure or Eliminated Water Supply Source:
  - Exclude all sources of water supply in the site where urination applies. Bluing substances must be putted in the toilet tanks and bowls to avoid specimen dilution.
- **S**ecure or Excluded Detergent Source:
  - Exclude all soap sources or any other potential adulterants.
- **S**ecure Sample Storage Area:
  - A secured collecting site area should be ready to proof sample security before to carry to the laboratory site.
- **S**ecure Documented Log Book:
  - A recorded log book must be ready to report collected samples.

Substances of Abuse Testing: (Specimen Collection)

Collection: Urine/Oral Fluid Sample Collection Protocol

Principle:

- The validity of urine sample substance screen results is dependent on sample integrity level.
- While direct-observation collections technique gives samples of the highest credibility, non-witnessed collections technique may be effective if collectors are in site to assure the donor does not have access to adulterant substances which may change test results value (tape water, adulterant chemicals substances, replaced urine, etc.).

Suggested Steps (Before To Collection):

- Ask for the identity of donor :
  - e.g. national security card or driver's license card and photo I.D. & If using a substance screen test request forum, report the identity data on the forum.
- Ask the donor case to get ride any unnecessary outer clothing:
  - All donor personal belongings (the material may retain a wallet) must be placed in a secure site outside the collecting site.
- Ask the donor case to empty his/her pockets or to remove articles of clothing such as shirts, dresses, etc.
  - ONLY If a collector repots any abnormal behavior that requires a donor case may attempt to adulterate a sample (e.g., abnormal bulging pockets), the collector personnel may ask that the donor empty his/her pockets and give the reason of the requirement for such articles during urine collection process.
- Ask the donor case to wash his/her hands by soap and water (before to collecting process):
  - To eliminate any possible adulterating materials or contaminating ingredient from under the suspected fingernails.

Urine Collection Procedure:

- Report the following data on the collecting bottle label:
  - Date of urine collection
  - Donor's name and/or identification card numbers
  - Collector's name
  - Case reported code number
- Give the donor with:
  - A clean, unused urine sample collecting container and order the donor to fill the collecting container at least half full (a minimum of 50 mL').

-Supervise the unobserved collecting procedure:

- Allow the donor case to enter and maintain privacy within partitioned collecting site. The collector personnel shall wait outside the collection site until the donor is finished from urine collection process. Complete the remaining data of the test request forum during the donor is obtaining the sample.

- Accept the sample from the donor.

- The use of disposable plastic gloves is mandatory when handling samples, so before to accepting the samples from the donor, be sure to wear plastic gloves.

-Detect urine sample's temperature:

- After accept of the urine sample from the donor, immediately put the temperature strip (if available) to the inside of the bottle. If reporting a substance screen investigating request forum, report the urine temperature degree on the forum.

NOTE: Urine temperature degree must be detected within (3) three minutes of collecting process and should read between 32-38 °C

NOTE: Observed Collecting Procedure: Inform the donor that collecting process shall apply under direct observation protocol. Accompany the donor into the collection site (the collector must be the same gender). Direct the donor to urinate into the urine specimen collecting container with the witness observing urination process direct protocol. Complete the remainder data of the test request forum after the donor has completed collecting the urine sample.

Specimen Validity:

Specimen Tampering/Adulteration

- Principle

Techniques to adulterate urine samples for drug abuse testing procedures generally represent in three procedures:

Urine substitution:

- The replacement of one's own urine specimen with one which is clean is a high incidence act. The best procedures to prevent this practice is to record urine temperature degree, as urine sample even held close to the body surface for extended durations of time will not give a physiologically normal temperature-correct sample.

Ingestion of fluids or compounds:

- For flushing out the urinary tract system, diluting the urine sample, or interfering with the testing procedure. Drinking large amount of liquid, especially juice of cranberry or pure vinegar is common act.

Although, procedures revealed these procedures have no action on testing pathways and may give unexpected informational results.

- Many of the substances being investigated are pH dependent substances. When large amount of juice of cranberry or pure vinegar are intake, the urine pH is decreased, and the rate of excretion of these substances may accelerate. If timed rightly, large volumes of a substances may excrete rapidly in the urine sample.
- One potentially effective procedure which may negatively affect the testing procedure is to intake large amount of water, as short term water loading volume can rise urine amount up to eight time. Therefore, if the individual's drug level is near the cut-off level of an assay panel, the urine status may be diluted enough so that the urine sample will detect below the cut-off level. Other reported procedures of adulteration involve consuming large quantities of vitamin C, vitamin B, niacin, Golden Seal, etc. All of these substances are useless acts.

Direct addition of adulterants:

- Direct adding of adulterants materials to the urine sample itself is the final technique to adulterate the laboratory procedures. Adulteration of a urine samples with various substances is reported to inactivate some of the laboratory testing procedures, especially, the enzymatic immunoassay's techniques.
- Adding of material such as alcohols, blood, sodium bicarbonate various soaps, sodium chloride, hydrogen peroxide, bleach, etc. are reported to lead to both pseudo negatives and pseudo positives.
- The recent list of adulterating material to urine sample is changing as the web sites gives an data source, as well as the effect for commercial products capable of changing the results of some urine drug testing procedure. Nowadays, nitrites kits (Klear and Whizzies) and chromates kits (Urine Luck) are two adulterating agents commonly detected in the field work. Saudi PCCs are capable of giving testing for these materials.

Adulteration & Dilution Detection:

- Means to identify adulteration techniques by the collector personnel and/or the laboratory technicians involve the following:

Specimen Temperature:

- Procedure:
  - If sample collecting process is not direct observed, the most effective procedures to detect sample dilution, adulteration, or replacement is to detect the sample's temperature degree.

The collector must measure the temperature degree utilizing the temperature strip indicator fixed to the sample container within FOUR minutes of collecting process; it must read between 32 and 38 °C.

- Documentation:
  - The urine temperature should be reported on Urine Test Request forum.
- Urine Appearance and Odour:
  - From odour:
    - Adulterants materials as soaps, bleach, isopropyl alcohol, and perfumes are readily detected by their characteristic odor.
  - From bubbling:
    - Soaps are also detected by marked bubbling appearance.
  - From residues:
    - Utilize of solid adulterants materials is identified by the appearance of residues substitutes in the collecting container.
- Specific Gravity:
  - Normal SGr = 1005 - 1035:
    - Normally, a randomly selected urine sample shall have a specific gravity of ( ) 1.005 & 1.035.
  - Low SGr <1.005
    - An very low specific gravity (<1.005) revealed a diluting attempt of urine sample,
  - High SGr >1.045
    - In the opposite side abnormally increase specific gravity (>1.045) may direct the collector to the presence of suspected dissolved solids adulterants as sodium chloride and sodium bicarbonate.
- pH:
  - Normal urine pH = 4.8-7.8:
    - Normal randomly selected urine sample pH is 4.8-7.8*.
  - Low urine pH < 4.8
    - Low urine pH's revealed possible intake of acidic material such as juice of cranberry or pure vinegar solution; condition of starvation ; severe diarrhea; or direct adulteration attempt of the sample itself with adding acidic materials.

- High urine pH > 7.8
    - Elevated urine pH's may indicate the presence of basic compounds such as sodium bicarbonate, bleach, or Drano; vegetarian diet; or prolonged vomiting.
- Visible Blood Detection:
    - Indication:
        - It indicates the presence of blood in the urine sample. The presence of blood in the urine sample may adversely affect the testing procedure and, in addition, material a biohazard for laboratory staff.
    - Precaution:
        - Collection of clean clear urine sample during menstruation period should be aimed.
- Urinary Creatinine Level:
    - Creatinine is a metabolic end product of muscle catabolism which normally excrete in urine flow in nearly fixed amounts over each 24 hour urinary daily excretory duration period. Therefore, urinary creatinine level can be utilized both as a indicator marker to specifically detecting a sample as urine biological sample, and as an indicator value of urinary water content level (dilution attempt).
    - Creatinine urinary level > 20 mg/dl:
        - Normal random selected urine sample will have urinary creatinine concentration of more than 20 mg/dL.
    - Creatinine level 10-20 mg/dl:
        - Samples with Creatinine concentration between 10 and 20 mg/dL may be rise from increased liquid intake, physiologically high water content dietary habits, or high amount of liquid ingestion behavior.
    - Creatinine urinary level 2-10 mg/dl:
        - Urine sample with creatinine concentration between 2 and 10 mg/dL are usually a result of intake of large amount of water (or other liquid substances), identified as short term water/liquid loading attempted.
        - This is a very common act when attempting to dilute a urinary sample so that any represented drugs in the urine sample will be diluted below analytical detecting testing cutoff concentration.
        - A critical item to put in mind when comment on dilute urine samples is that drug use shall be never be

detected unless specifically detected, and confirmed in a urine sample. Specifically, a dilute urine sample shall produce pseudo negative results, as drugs in the urine at concentrations level near the testing cutoff level or may be diluted below the testing cutoff concentration, although, due to the causes documented above it can be difficult to prove the cause or intent for the urine sample(s) being dilute.

- Creatinine urinary level <2 mg/dl:
    - Urine Creatinine concentration below 2.0 mg/dL are usually a result of the direct addition attempt of a water and/or liquid substance to the urine sample.
- Creatinine urinary level 0 mg/dl:
    - Creatinine urinary concentration of 0.0 mg/dL mean the sample is not consistent with normal human urine sample constitute.

✓ NB: Urine samples become dilute as a result of the short duration intake of large volumes of a water and/ or liquid due to an unknown excitatory factors such as a physiologically response to heat exposure or exercise activities, herbal flushing effects, diuretics medication prescription, intentional dilution attempts, or pathological conditions such as diabetes insipidus syndrome.

✓ NB: The dilution act from taking high volumes of water and/or liquid can present from two – five hours. Therefore, the raised consuming of water and/or liquid should have to perform between two – five hours before to the collecting process of the urine samples.

✓ NB: For these causes, urine creatinine concentration is recorded in combination with detecting for drugs of abuse, as an indicator marker of sample validity condition only, as urine sample with a creatinine concentration below 20 mg/dL may have a rising attempt of leading a pseudo negative drug testing result.

✓ NB: Normal mentioned ranges are reported only for freshly voided urine samples.

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ASYMPTOMATIC PATIENT PRESENTATION:

I- BASICS:

Description:

- Although consuming a life-threatening substances intake, a patient may be initially asymptomatic or have minimal reported manifestations that recover and thereby misdirect the physician.

II- DIAGNOSIS:

i- Toxic substances exposure with no initial effects:

Acetaminophen

- 12 - 48 hours: Hepatic impairment associated with gastrointestinal manifestations as, nausea, vomiting, right upper quadrant pain, and laboratory finding abnormalities consistent with toxicity of the liver shall be apparent.
- Renal and pancreatic impairment also may occur.

Anticoagulants

- Anticoagulants (warfarin, pindone, valone, brodifacoum, chlorophacinone, diphacinone, pivalyn).
- 24 hours to several days: Clinical manifestations of bleeding (epistaxis, hematemesis, bleeding gums) accompanied with an increased prothrombin time on laboratory findings may detect.

Arsenic or Thallium

- Days to months: Gastrointestinal upsets usually develop within 1 to 2 hours in acute intoxication. Repeated small arsenic doses exposures shall lead to delayed manifestations days or weeks later (water contamination, homicidal attempts).
- Repeated small doses will reveal to delayed toxic manifestations days or weeks later from the time of onset time of exposure (water contamination, homicidal acts).

Body Packers

- Hours to days: The category of manifestations depends upon the substance ingested; heroin and cocaine are the commonest reported.
- Time of manifestations onset varies with the type packaging utilized; in cases of body packers, they wrap packed drugs carefully, but the packets contain huge amounts of addicted substance per package, resulting in fast and severe development of manifestations once a package breaks, tear or leaks.

Button (Disk) Battery

- Hours to days: Battery may split or leak during transit pass through the gastrointestinal tract system.

- Manifestations may occur suddenly at any time when the battery breaks and accept the caustic substances contents to release.

Ethylene Glycol

- 8-24 hours: Severe metabolic acidosis condition, tachycardia, tachypnea, and renal impairment may occur after an initial asymptomatic stage following exposure of Ethylene Glycol.
- The metabolic acidosis require several hours to start.
- If the patient has exposed to ethanol as well, manifestations may be postponed further still until the exposed ethanol amount has been completely metabolized

Hydrofluoric Acid

- Immediate to 12 hours: Low-concentration (6%-8%) cutaneous hydrofluoric acid damage may locate hours after the onset of exposure to low-concentration components.
- Dermal Manifestations can appear minimal even when damage and painful sensation are high.

Lead

- Hours to weeks: Acute exposure by ingestion of lead curtain weights, sinkers, etc. may develop delayed neurological manifestation as encephalopathy and death in pediatrics.

Methanol

- 6-24 hours: Severe metabolic acidosis condition with a disturbed consciousness level, tachycardia, tachypnea, and irreversible blindness may occur after an initial asymptomatic state following methanol ingestion.
- The acidosis develops at least 9-12 hours to occur.
- If the patient has co-ingested ethanol with methanol, manifestations may be postponed more still until the ingested ethanol amount has been completely metabolized.

Mercury

- Hours to months: A single exposure to mono- or dimethyl mercury (either cutaneous or through ingestion) has leaded to delayed neurologic and renal toxic manifestations.

Naphthalene

- 1-7 days: Manifestations of hemolysis with hyperthemia, vomiting, abdominal pain, diarrhea, lethargy, jaundice, and dark coloured urine are typically postponed after ingestion as naphthalene is metabolized to its active hemolytic metabolite ingredients.

Oral Hypoglycemic

- Oral hypoglycemic agents (glipizide , glyburide, tolazamide [Tolinase], acetohexamide, chlorpropamide, tolbutamide).
- 2-12 hours: The onset of hypoglycemic manifestations may be postponed, especially with long-acting medications such as chlorpropamide, which may have a delayment in peak concentrations of up to 36 hours.
- It is recommended that the random blood glucose level be monitored for 12-24 hours following exposure of an unknown oral hypoglycemic medications.

Snakebite (Coral Snake, Rattlesnake)

- Immediate to 12 hours: Neurologic manifestations following coral snake bite may be postponed.
- Swelling, edema, tenderness, ecchymotic patches, and coagulopathy tendency of rattlesnake bite toxicity may be postponed 4-12 hours.
- Dependent resting positioning of an intoxicated limb may postpone venom absorption and the onset of toxic manifestations.

Sustained-Release Products

- Includes active ingredients products such as (e.g., aspirin, theophylline, propranolol, lithium, and verapamil.)
- Up to 24 hours: Postponed absorption and toxic manifestations may develop due to the constitution of these active ingredients.
- Manifestations vary with the type of intoxicated active ingredient substances.

ii- Toxic exposure with minimal initial symptoms:

Antineoplastic agents

- Hours to days: Most antineoplastic medication shall lead to some gastrointestinal upset manifestations within several hours of intake; however, bone marrow depression, the major toxic category of most medications, may not occur for several days from exposure.

Cadmium

- Up to 96 hours: After the recovery of initial manifestations, including mild cough, precordial and chest pain, dyspnea, shortness of breath, nausea, malaise and hyperthermia, a patient inhaling cadmium fumes during welding work may progress to delayed onset pulmonary edema.

Carbon Tetrachloride

- 1-3 days: Gastrointestinal upset, nausea and headache may develop early.
- Hepatic impairment, damage up to necrosis develops 1-3 days after the onset of carbon tetrachloride exposure.

Cement

- 12-24 hours: Cutaneous exposure to wet form of cement (calcium hydroxide) may develop in dermal damage and skin ulceration as cement substance leaks around boots or gloves.
- Manifestations do not start for several hours from the time of exposure.

Chlorine

- Up to 24 hours: After initial manifestations of respiratory passage irritation subside, pulmonary edema may occur following high level inhalation exposure.
- Some manifestations such as an intermittent mild cough are likely to remain in these patients.

Colchicine

- 2-12 hours: Gastroenteritis usually occurs within hours.
- Bone marrow depression occurs 4-5 days following exposure.

Hydrocarbons

- Up to 6 hours: Aspiration chemical pneumonitis may develop following hydrocarbon orally exposure.
- The diagnosis of an initial chest radiographic investigations may be normal with the delayed development of chemical irritant infiltrates several hours later associated with increasing respiratory distress signs and symptoms.
- A persistent mild cough episodes may be the only sign of chemical hydrocarbon aspiration during the otherwise asymptomatic stage.

Iron

- 6-24 hours: Following a gastrointestinal upset stage involving nausea, vomiting, diarrhea, and abdominal pain, patients may pass to improve for several hours following orally exposure before developing systemic toxic manifestations, including hypovolemic shock, pallor, generalized lethargy, metabolic acidosis, and coagulopathic manifestations.

Paraquat

- Immediately to days: High-concentration of paraquat ingestion produces initial caustic gastrointestinal manifestations.

- Lower concentration of paraquat oral or cutaneous exposure may occur with renal impairment over 3-5 days and diffuse pulmonary fibrosis over 1-2 weeks.

Phosgene

- Up to 72 hours: Initial irritant respiratory and neurological manifestations of cough, dyspnea, irritability, and anxiety may be delayed following phosgene exposure to concentrations level of less than 3 ppm.
- Pulmonary imitation and edema may be postponed for as long as 72 hours following inhalation exposure.

III- Treatment:

- A common approach to intoxication includes close patient observation and performing indicated investigations.
- Knowledge of the specific poison facilitates detecting an appropriate duration of medical close observation as well as indicating appropriate laboratory tests panel. (In-dividualialized Laboratory testing detection)

IV- Pitfalls:

Treatment

- Due to the low incidence of late developed complications of poisonous ingestion, some physicians have a false sense of security.
- Asymptomatic patient's presentation may be premature discharged before more serious manifestations develop.

REFERENCES:

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2. *Hoffman RS, Howland MA, Lewin NA, et al. (eds.)(2014): Goldfrank's Toxicologic Emergencies, 10th ed. New York: McGraw-Hill.*
3. *Tintinalli JE, Stapczynski JS, Ma OJ et al. (eds.)(2010): Emergency Medicine: A Comprehensive Study Guide, 7th ed. New York: McGraw-Hill,.*
4. *Klaassen, Curtis; Watkins III, John B. (2015). Casarett & Doull's Essentials of Toxicology, Third Edition (Lange). McGraw-Hill Education.*

MEDICAL TOXICOLOGY HISTORY INTAKE FORM

PLEASE PRINT

First Name:	Last Name:	Middle Name:	Date:
Street Address:	City:	Home Phone:	
Date of Birth:	Marital Status:□M □S □W □D	Sex: □M / □F	ID/Iqama number
Name of Primary Care Provider:		Phone of Primary Care Provider:	

REASON FOR SEEKING CONSULTATION WITH A MEDICAL TOXICOLOGIST

CURRENT PRESCRIPTION MEDICATIONS / OVER-THE-COUNTER MEDICATIONS / HERBS & SUPPLEMENTS

List all prescription, non-prescription, herbal medications, and supplements taken.

Prescription Medication	Strength	Times per Day	When Started

Non-Prescription Medications	Strength	Times per Day	When Started

ALLERGIES or REACTIONS TO MEDICINES/FOODS/OTHER AGENTS:

Medication/Food/Other Agent	Side Effect

PAST MEDICAL HISTORY:

Please check (√) if YOU have ever seen a physician for or been treated otherwise for any of the following medical conditions

□ Substance Abuse	□ Allergies	□ Bleeding Problems
□ Bulimia/Easting Disorder	□ Cancer (please specify)	□ Depression
□ Diabetes	□ Heart Disease	□ High Blood Pressure
□ Endocrine/Hormone Disorders (e.g., thyroid, low testosterone)		□ Lung Problems
□ Kidney Disease	□ Liver Disease	□ Hearing impairment
□ Neurological Disorders (e.g., tremor, stroke, blindness, seizures, coma,numbness, weakness, migraine)		
□ Chronic Pain	□ Psychiatric Problems (e.g., bipolar disorder, schizophrenia)	
□ Rash/Allergy	□ TB	□ Other (Please specify below)

Please provide details for all checked boxes:

SURGICAL HISTORY

(Please list all prior operations or surgical procedures and dates):

SOCIAL HISTORY:

Please check (√) all that apply:

SMOKING		
□ Current Cigarette Smoker	□ Former Cigarette Smoker	□ Never Smoked
ALCOHOL USE		
□ Currently using	□ Used to drink alcohol	□ Never drink alcohol
RECREATIONAL DRUG USE		
□ Current Drug User	□ Former Drug User	□ Never Drug User
□ Marijuana	□ Cocaine	□ Ecstasy	□ Methamphetamine
□ Heroin	□ Designer Drugs	□ LSD	□ Glue Sniffing
□ IV Drugs	□ Other (Please specify)		

EDUCATION COMPLETED:

□ Grade school □ High school □ Univ. □ Post Graduate education.

Total Years of education: .....

FAMILY HISTORY:

Please check (√) if your (parents, siblings) has a history of any of the following:

□ Alcohol / Drug Problems		□ Allergies	□ Bleeding Problems
□ Other blood diseases	□ Cancer (please specify type)		□ Diabetes
□ Endocrine/hormone (e.g., thyroid)		□ Heart Disease	□ High Blood Pressure
□ Kidney Disease	□ Liver Disease	□ Lung Problems	□ Rash
□ Neurological Disorders (e.g.tremor, stroke, coma, blindness)			□ TB
□ Psychiatric Problems (e.g., depression, bipolar disorder, schizophrenia)			
□ Other (Please specify)			
Please provide details for all checked boxes:			

OCCUPATIONAL HISTORY

- Any Exposure to Vapors Gas Dusts or Fumes (specify):
  .....
- Is there something you were exposed to that you are concerned about? □ Yes: ..... □ No: .....
- Do you use protective equipment such as gloves, masks, respirator, or hearing protectors in the workplace? □ Yes: ..... □ No: .....
  If yes, please list the protective equipment used:.....

REVIEW OF SYSTEMS:

Please check (√) any current problems you have on the list below.

□ Constitutional	□ Fevers/chills/sweats	□ Fatigue/weakness	□ Allergies
□ Unexplained weight loss/gain		□ Eyes	
□ Excessive thirst or urination			
□ Change in vision (blurry vision or decreased vision)		□ Difficult hearing/ringing in ears	
□ Ears/Nose/Throat/Mouth	□ Problems with teeth/gums	□ Difficulty tasting with food or drinks	
□ Cardiovascular			
□ Leg pain with exercise	□ Chest pain/discomfort	□ Palpitations or irregular heart beat	
□ Chest (breast)	□ Breast lump/discharge	□ Female □ Lactating □ Pregnant	
□ Respiratory			
□ Cough/wheeze	□ Difficulty breathing		
□ Gastrointestinal			
□ Abdominal pain	□ Blood in bowel movement	□ Nausea/vomiting/diarrhea	
□ Reflux or gastritis	□ Ulcer		
□ Genitourinary			
□ Frequent nighttime urination	Leaking urine	Unusual vaginal bleeding	
□ Discharge: penis or vagina	Sexual function problems	Musculoskeletal	
□ Sexually transmitted disease			
□ Muscle/joint pain			
□ Joint swelling or inflammation	Arthritis	Rheumatoid arthritis	
Skin			
□ Hives / Eczema or Rash	□ Chemical Sensitivity	□ Abnormal bleeding or bruising	
□ Easy bruising/bleeding	□ Unexplained lumps		
Neurological			
□ Headaches	□ Dizziness/light-headedness		
□ Numbness in hands, feet, fingers or other areas (specify please)			
□ Memory loss	□ Loss of coordination	□ Difficulty walking	□ Tremors or shaking
Other "nervous" condition".....			
.....			
.			
Psychiatric			
□ Anxiety/stress	□ Hallucinations	□ Depression	□ Blood/Lymphatic
□ Other (please specify)			
Please provide details for all checked boxes:.....			
.....			
.....			

ENVIRONMENTAL EXPOSURES HISTORY:

Please check (√) If you live or have ever lived next door to or very near any of the following facilities:

□Industrial Plant □Commercial Business □Waste Dump Site

Have you been out of the country during the past year? □ Yes □ No

If Yes where?.....

Attending Physician`s Signature.....

REFERENCES:

1. *California PCC Antidote Chart (2014), http://www.calpoison.org/hcp/Antidote_Chart_2014, 1014.*
2. *Goldfrank, L. R., & Flomenbaum, N. (2010). Goldfrank's toxicologic emergencies. New York: McGraw-Hill.*
3. *Olson, K. R., & California Poison Control System. (2006). Poisoning & drug overdose. New York: Lange Medical Books/McGraw-Hill.*
4. *Illinois Poison Center Antidote List (2013), http://illinoispoisoncenter.org /ipc_media/pdf/antidote%20list%202%202011.pdf*
5. *Poison Information Center of Ireland antidote list (2011), http:// www.poisons.ie/ Downloads/Antidote_Booklet_2011.pdf*
6. *KSA. MOH Formulary Drug List (2014)*
7. *Lheureux PE, Zahir S, Gris M, et al. 2006: Bench-to-bedside review: hyper-insulinaemia /euglycaemia therapy in the management of overdose of calcium-channel blockers. Crit Care;10 (3):212*
8. *Young AC, Velez LI, Kleinschmidt KC, 2009: Intravenous fat emulsion therapy for intentional sustained-release verapamil overdose. Resuscitation; 80 (5):591–3.*
9. *Buckley NA, Eddleston M, Li Y, et al, 2011: Oximes for acute organophosphate pesticide poisoning. Cochrane Database Syst Rev Feb 16;(2):CD005085.*

ANTIDOTES CHART

Availability requirements (AR):

(A): Required to be immediately available (within the Emergency Department) ,

(B): Required to be available within 1 hour (within the hospital),

(C): These drugs are rarely used and can be held supra-regionally.

Antidote	Toxin	Dose	AR*	NOTES	P or Not P**
Acetylcysteine (NAC)	-Acetaminophen Poisoning -Chloroform Poisoning - Carbon Tetrachloride Poisoning - Other Hepatotoxins	- IV NAS 20 hour's course: Loading dose 150 mg/kg over 1 hour followed by 50 mg/kg over 4 hrs followed by 100 mg/kg over 16 hrs. - IV NAS 48 hour's course: Loading dose 140 mg/kg followed by 70 mg/kg over 4 hrs. for 12 doses - Oral NAS: Loading dose 140 mg/kg followed by 70 mg/kg every 4 hrs. for 17 doses.	A	- Beware anaphylactic reaction (bronchospasm, hypotension, wheals, and laryngeal edema) during IV administration. - IV NAC may be preferable in patients who have hepatic encephalopathy or are pregnant.	P

Activated charcoal	- Most poisons. Up to one hr. following ingestion. - It may also be considered more than one hr. after ingestion in some poi-soning as Theophylline	**Initial dose**: 1 g/kg (adult dose 50–100 g; child < 5 years,10—25 g) orally or by gastric tube **Repeated-doses:** 15–30 g (0.25–0.5 g/kg) every 2–4 hours or hourly (adults, average rate of 12.5 g/h; children, rate of 0.2 g/kg/h) is given orally or by gastric tube.	**A**	Contraindication in: alcohols, caustics, cyanide, iron, hydrocarbons, lithium and coma without airway protection	**P**
Atropine	- Organophosphate / Carbamates insectcide poisoning & other cholinester-ase inhibitors e.g., warfare agent - Bradycardia indu-ced by a variety of drugs.	- In cholinesterase inhibitor poisoning (OPI) adult: 1 to 3 mg IV; children: 0.02 mg/kg IV. Three to five minutes after giving atropine, check the pulse, blood pressure, pupil size, sweating and chest sounds. If no response, double the dose and continue doubling the dose q 3 to 5 minutes when the response is still absent. Once the parameters have begun to improve, cease dose doubling. Similar or smaller dose can be used as required to dry pulmonary secretions. Once secretions are dried, maintain with an infusion of 10% to 20% of the loading dose every hour. - Drug induced bradycardia: 0.5-1 mg IV for an adult (0.02 mg / kg for a child)	**A**	- May require large amounts in severe cholinesterase inhibitor poisoning (oxygen should be provided at the first). - 3 mg is a fully vagolytic dose in adult.	**P**

*** (AR) Availability requirements - ** Purchasable By MOH (P by MOH) Or Not Purchasable By MOH (Not NP by MOH)**

Antidote	Toxin	Dose	AR*	NOTES	P or Not P**
Antivenom (Polyvalent and bivalent) for Snake bite	Snake envenomation - Any local or systemic signs are an indication for antivenin administration. - Polyvalent snake antive-nin for heamatotoxic snakes. - Bivalent snake antivenin for neuro-toxic snakes.	- Haemotoxic: Polyvalent antivenom 5 amp dilutes in 250ml saline given over 60 min & can be repeated every 4-6hrs until improvement - Neurotoxic: Bivalent antivenom 5 amp diluted in 250 ml saline, more antivenom should be given if sever signs persist after 1-2 hrs. and dose can be repeated every 4-6 hrs. until improvement. N.B. double the dose of the polyvalent antivenom if bivalent not available	A	- Initial sensitivity test. - Give antivenin in IV drip diluted antivenin 1/1 up to 1/10 in isotonic normal saline. - Be ready to treat anaphylaxis. - Children dose = adult dose.	P
Antiscorpion	Scorpion envenomation	Initial dose: 5 amp polyvalent antiscorpion diluted in 20 - 50 ml saline given IV over 20 minutes (min.). If systemic manifestations still exists the same dose can be repeated every 2 hrs. up to 4 doses.	A	- Initial sensitivity test - Should be given very early - Keep the patient under observation for at least 24 hrs. after recovery	P

BAL (Dimercaprol)	Heavy metals poisoning In lead encephalo-pathy: It is used only with conjunction of calcium EDTA therapy.	2.5-3 mg/kg by deep IM every 4-6 hrs for 2 days, 2-4 times daily on the third day and then 1-2 times daily for 10 days or until recovery	**C**	- IM administration only - Changing it to oral succimer once patient is stable and able to absorb. oral formula	**P**
Benzodiaze-pines	-Drugs cause convuls-ions, anxiety and agitation. -Treatment chloroq-uine and cocaine cardiotoxicity - Alcohol or sedative-hypnotics withdrawal.	- Diazepam: 0.1-0.3 mg/Kg may repeat if needed. - Lorazepam: 0.05-0.1 mg/Kg may be repeated. - Midazolam: 0.1-0.2 mg/Kg may be repeated. - In Chloroquine toxicity 2 mg/kg IV over 30 mins in combination with assisted ventilation.	**A**	- Excessive or rapid IV administration may cause respiratory arrest.	**P**
Benztropine	- Acute dystonic reactions associated withof neuroleptics or metoclopramide	1-2 mg IV or IM (children 3 years old, 0.02 mg/kg, maximum 1 mg). Repeat the dose within 15 min if there is no response. Same dose may be given orally every 12 hrs. for 2-3 days to prevent recurrence of symptoms	**A**	- It is an alternative in adults to diphenhydr-amine (the drug of choice for children). - It is not effective for dyskinesia or NMS.	**P**

*** (AR) Availability requirements - ** Purchasable By MOH (P by MOH) Or Not Purchasable By MOH (Not NP by MOH)**

Antidote	Toxin	Dose	AR*	NOTES	P or Not P**
Botulism antitoxin & Baby Botulism IG (BIG)	- Botulinum antitoxin, heptavalent for botulism in child >1 Y & adults. - Botulism immune globulin, human (BabyBIG) for infant botulism < 1 Y	Adult: one vial 10 ml diluted in 0.9% Saline and given by slow IV infusion. A second vial may be given 2-4 hrs if symptoms worsen. Child 1 to 17 years: 20 to 100 % of the adult dose. Infant <1 year: 10 % of the adult dose.	C	- Initial sensitivity test. - Ready to treat anaphylaxis -The antitoxin should be given as soon as possible and not delayed while awaiting results of diagnostic studies	N P
Bromocriptine	Neuroleptic malignant syndrome (NMS) caused by neuroleptic drugs	Adult: 2.5-10 mg orally 2-6 times daily. Pediatric dose is unknown. Use small, frequent dosing to minimize nausea	B	- Continue treatment until rigidity ant fever have completely resolved.	P
Calcium (Calcium Chloride & Calcium Gluconate)	**Calcium channel blocker** **I èǈ2ǒl-ťőŜY ʎl- ʎyŘǳǑŜŘ õè** (fluoride, oxalate or the IV anticoagulant citrate, ...) Hydrofluoric acid toxicity. **Severe hyperkalemia** with cardiac manifestations (not digoxin induced). **Black widow spider.**	Adults: Give 3 g Ca gluconate (30ml of 10% solution) or 1g Ca chloride (10ml of 10% Solution). This dose may be repeated every 5-10 min., as needed. It can be given as a continuous infusion 20-50 mg/kg/hr. Children: 60 mg/kg (0.6 ml/kg of 10% solution)	A	- Can cause tissue necrosis if extravasation occurs - Not used in digoxin toxicity. - Calcium chloride contains nearly three times the amount of Ca^{2+} per mL of 10% solution compared with the same concentration of calcium gluconate. - Use central line for Calcium chloride	P

Calcium Gluconate Gel	Hydrofluoric acid skin exposure burns < 5% of body surface or exposures to concentrations of < 20%	2.5-33 % concentration	**A**	- Manufacture of topical gel For topical burns	
Carnitine (L-Carnitine)	Hyperammonemia from valproic acid toxicity	50–500 mg/kg/d. - A loading dose equal to the daily dose may be initially given, followed by the daily dose divided into every 4 hrs. doses. - A maximal daily dose is 3 g/day.	**A**	Transient nausea and vomiting are the most common side effects of L-carnitine	**P**
Cholestyr-amine	-Chlorinated hydrocarbons - Digitoxin - Amiodarone - Oral anticoagulants -NSAIDs - β. blockers - Thiazide diuretics - Oral hypoglycemic	- Adult: 4 g three times daily - Children 6-12 years: (Childs weight in kg X adult dose) / 70 - Children under 6 years: No dosage established.	**B**	Rarely used. (Rarely prescribed for children).	**P**

*** (AR) Availability requirements - ** Purchasable By MOH (P by MOH) Or Not Purchasable By MOH (Not NP by MOH)**

Antidote	Toxin	Dose	AR*	NOTES	P or Not P**
Cyanide Antidote Kit (Conventional)	- Cyanide poisoning - Hydrogen cyanide (HCN) - Sodium nitroprusside, Bromates (thiosulfate only) - Hydrogen sulfide (H2S) (nitrites only)	Adult: - Amyl nitrite crush ampoule in gauze and place under the nose of the victim for 30 seconds every min. Use a new ampoule every 2-3 min. - Sodium nitrite 300 mg (10 ml of 3% solution) over 3.5 min. -Sodium thiosulfate 12.5 g of 25% sol slowly IV Children: sodium nitrite 0.15-0.33 ml/kg Sodium thiosulfate 1.6 ml/kg of 25% solution.	Sodium Nitrite & Sodium Thiosulfate **A**	Kit contains (2-10mL (3%) amps of sodium nitrite, 2-50 mL (25%) vials of sodium thiosu-lfate, 12 amyl nitrite inhalant amps). Stocking this kit may be unnecessary if an adequate supply of hydroxyl-cobalamin HCl is available	**N P**
Cyanokit Hydroxycobalamin	- Cyanide & HCN poisoning - Smoke Inhalation Victims (CO, H2S)	5 g as intravenous infusion over 15 min. Depending on severity of poisoning, 5 g may be administered as a second dose.	**A**	Newer, safer and easier to use than the cyanide kit	**N P**
Cyproheptadine	Serotonin syndrome caused by: - Monoami-ne oxidase inhibitors - Selective serotonin reuptake inhibitors	Adults: Initially: 12 mg p.o. and then 2mg every 2 hrs. if symptoms continue. Maintenance: 8mg every 6 hrs. Children: 0.25 mg/kg/d divided every 6 hrs. with a maximum of 12 mg/d.	**B**	It is only available in oral form, but tablets may be crushed and administer-ed by nasogastric tube.	**N P**

Dantrolene	Hyperthermia from (malignant hyperther-mia, neuroleptic malign-ant syndrome, seroton-in syndrome, cocaine and amphetamines)	1mg/kg by rapid IV injection, repeated as required to a total dose of 10mg per kg. The average effective dose is about 2.5 mg per kg. Then 1–2 mg/kg IV should be given every 6 hrs.	**B**	IV administration can cause venous irritation and thrsombophlebitis	**P**
Defero xamine	Iron poisoning	IV route (15 mg/kg/hrs.). Continue desfe-rrioxamine until the patient is asymptomatic, resolved anion-gap metabolic acidosis and Iron level is <54 micromol/L.	**B**	Side effect: hypotens-ion, auditory, ocular, pulmonary toxicity, and infection.	**P**
Dicobalt edetate	Cyanide toxicity The antidote of choice in severe cases when there is a high clinical suspicion of cyanide poisoning e.g. after cyanide salt exposure.	300 mg by IV injection over about 1 min. repeated if the dose is inadequate; a further dose of 300 mg may be given 5 min. later if required. Follow each injection with 50mls of 50% dextrose intravenously. **NB.** Only one of three cyanide treatment options (Dicobalt edetate/ hydroxocobalamine/ sodium nitrite, sodium thio-sulphate) is required to be available	**A**	If symptoms of cobalt toxicity occur (nausea, vomiting, urticarial rash, chest pain, bronchospasm, hypotension, co-nvulsions, tachycardia, ventricu-lar arrhythmias and periorbital oedema), stop administration of the drug and institute supportive measures immediately.	

*** (AR) Availability requirements - ** Purchasable By MOH (P by MOH) Or Not Purchasable By MOH (Not NP by MOH)**

Antidote	Toxin	Dose	AR*	NOTES	P or Not P**
Intravenous lipid emulsion (Intralipid)	Lipophilic cardiotoxic agents (Local anesthetics and possibly other cardiac toxins e.g., CCB, buprop-ion, cocaine, β. B., TCA)	1.5 mL/kg of 20% intralipid as an initial bolus followed by 0.25 mL/kg/min for 30–60min. Depending upon response, bolus could be repeated 1-2times and infusion rate increased.	A	ILE: contraindicated in patients with known egg allergies, disorders of fat metabolism, and liver disease.	P
Digoxin Immune FAB Digibind or DigiFab®	Digoxin poisoning; other cardiac glycosides (eg, oleander, foxglove)	Acute toxicity: Adults (and children > 20kgs): No. of vials= Serum Digoxin (ng/mL) × Pt Wt (kg)/100 No. of vials= Amount ingested (mg) × 0,8/0.5 Infants and children <20kgs: Dose of digifab (mg) = 0.40 X serum digoxin level (ng/ml) X Body weight (kgs)	B	Consult with poison center regarding dosing	P
DMSA (Succimer)	Heavy metal poisoning (Arsenic, Lead , Lewisite, Mercury)	10 mg/kg 3 times a day for 5 days followed by 10 mg/kg twice a day for 14 days.	C	Succimer can be combined with CaNa2EDTA to take advantage of the ability	P

EDTA-Calcium	Heavy metal poisoning (Lead toxicity, Zinc salts)	For patients with lead encephalopathy: 1500mg/m2/d* by continuous IV infusion starting 4 hrs. after the first dose of BAL Then Concurrent BAL and EDTA therapies are administered for 5 days *M2 is calculated as follows: BSA = SQRT(cm*kg)/3600)	**C**	Side effect: Renal toxicity The combination of EDTA with succimer appears more potent	**N P**
Ethanol IV 10% with 5% Dextrose and Ethanol (oral)	- Methanol toxicity - Ethylene glycol toxicity	- Loading Dose: 0.8 g/kg of 10% ethanol (infused over 1 hrs. as tolerated) - Maintenance Dose: 110 mg/kg/hr. Chronic Alcoholic: 150 mg/kg/hr. During Hemodialysis: 250 mg/kg/hr. In oral use 20% ethanol	**B**	IV 10% ethanol product no longer manufactured. Fomepizole easier to dose and monitor than ethanol	**N P**
Fomepizole	- Methanol toxicity -Ethylene glycol toxicity	Loading Dose: 15mg/Kg over 30 min, Followed by 10mg/Kg q 12hrs. for 4 doses, then if necessary, 15mg/Kg q 12hrs. until the pH is normal and methanol level <20mg/dl.	**B**	Fomepizole is the antidote of choice. Ethanol only needs to be held if fomepizole is unavailable.	**N P**

*** (AR) Availability requirements - ** Purchasable By MOH (P by MOH) Or Not Purchasable By MOH (Not NP by MOH)**

Antidote	Toxin	Dose	AR*	NOTES	P or Not P**
Flumazenil	Benzodiazepine poisoning: Reversal of iatrogenic over-sedation with benzodiazepines.	Adults: Initially 0.1-0.2mg IV over 30 seconds. If there is no response within 30 seconds, then a 2nd dose of 0.3mg can be administered over 30 sec. Further doses of 0.5mg can be given over 30 sec, at 60 second intervals, to a total dose of 3mg. If there is still no response, it is unlikely flumazenil will reverse the CNS/resp depression. The infusion rate is 0.1-0.5mg/hr.; Adjusted to maintain the desired response. Children: A dose has not been recommended in children, the following has reversed coma in an overdose situation: 10mcg/kg IV not more	A	Use small initial dose to avoid abrupt awakening/ delirium. Do not uses in cases that are on chronic BZ therapy as withdrawal seizures may occur. Should not be used as a "diagnostic" agent and is contraindicated in mixed drugs overdoses (e.g. TCA/ BZ) and in cases with history of epilepsy.	P
Leucovorin (Folinic Acid) and Folic Acid	Methanol Toxicity -Folic acid antago-nist (e.g. Methotrexate, trimethoprim)	50 mg of IV folic acid every 6 hrs. for the first 24 hrs. and should be continued until the methanol and formate are eliminated. In Methotrexate give a dose equal to or greater than the dose of methotrexate given.	B	Should be administered at the first suspicion of methanol poisoning and within 1 hr. of methotr-exate poisoning	P

100% O2 and Hyperbaric oxygen (HBO)	- Carbon monoxide - Cyanide poisoning - Hydrogen sulfide - Carbon tetrachloride - High met Hg level unresponsive to methylene blue	Indications for HBO: - Significant CO poisoning with syncope, seizures, coma, lactic acidosis, myocardial ischemia, myocardial infarction, or abnormal psychometric testing - COHb level >25% in non-pregnant patient - COHb level >20% in pregnant patient - Evidence of fetal distress due to CO poisoning during pregnancy. - Significant cyanide or cyanogenic compound.	**A** for 100% O2	The optimal dose of HBO, number of treatments and treatment pressure, and the time after which it is no longer an effective therapy are not yet clearly defined. Consult PCC to determine if HBO treatment is indicated.	**P for O2 100%**
Methylene Blue	Methemoglobinemia	1–2 mg/kg IV given over 5 min., may be repeated Do not exceed total dose of7mg/kg	**A**	It is ineffective in patients with (G6PD) deficiency	**N P**
Mesna	Reduction of uroth-elial toxicity in anti-neoplastic therapy (Cyclophosphamide)	IV preparation: Adults: Doses are dependent on the amount of cyclophosphamide taken. It is 20% of cyclophosphamide taken, in Children or high-risk patients: Doses of up to 40% Oral preparation: Doses must be doubled	**B**	Urinary output should be maint-ained and monitor for hematuria and proteinuria throughout treatment but frequent bladder emptying should be avoided	**P**
Methionine	Paracetamol poisoning	Adult and children <6 Y: 2.5 grams initially followed by three doses of 2.5g every 4 hrs. Child < 6 Y: 1 g initially followed by three further doses of 1g	**No AR***	No longer considered essential because of its short time span of efficacy It can cause vomiting	

*** (AR) Availability requirements - ** Purchasable By MOH (P by MOH) Or Not Purchasable By MOH (Not NP by MOH)**

Antidote	Toxin	Dose	AR*	NOTES	P or Not P**
Naloxone/ Narcan	Opioid overdose	Adults: 0.05 to 2 mg IV for as bolus dose (0. 01 mg/kg for children). May be repeated every 2-3 min as necessary until the level of consciousness and respiratory rate increase A total dose (10-15 mg) may require.	A	Use small initial dose to avoid abrupt awakening/ withdrawal and convulsions. Re-sedation can occur within 1-2 hrs. Repeated doses of naloxone may be required	P
Octreotide acetate/ Sandostatin	Hypoglycaemia induced by sulphon-ylureas and quinine	Adults: 50 to 150 µg IM, or SC, injection q 6 hrs. Children: 1 - 1.5 µg/kg (up to 150 µg) q 6 hrs.	B	Avoid long-acting depot products. It may also given IV bolus over several min. or by continuous IV infusion	P
Physostigmine	Anticholinergic poisoning, especially antimuscarinic delirium	Adults: 1–2 mg Children: 0.02 mg/kg (maximum: 0.5 mg) IV infused over at least 5 min. The dose can be repeated in 10–15 min. Not generally recommended for children. Call PCC due to contraindication with usage.	A	Give at low dose, over 2-5 min. to avoid severe adverse reactions including bradycardia, a systole, and seizures. Contraindicated in TCA or similar poisoning with widened QRS intervals	P

Oximes Pralidoxime (2-PAM Protopam Obidoxime	Cholinesterase Inhibitor poisoning (organophosphate or "nerve gas")	**Pralidoxime:** 1-2 grams IV (or 30 mg/kg) over 30 min. followed by an infusion of 500 to 1000 mg/hr. (or 8 mg/kg per hr.). Children loading dose 25 to 50 mg/kg (2 g maximum) followed by infusion of 10 to 20 mg/kg per hr. **Obidoxime** (toxogonin): 250 mg amp; For adult give 1 amp over 15-30 min IV as a loading dose then 30mg/hr.	**C**	Oximes should be administered slowly, since rapid administration has been occasionally associated with cardiac arrest.	**P**
Protamine Sulphate	anticoagulant effects of unfractionated heparin (UFH) and for some of the effects of low molecular-weight heparin (LMWH)	Dose according to quantity of heparin: 1mg of protamine will neutralize approximately 100 units (1 mg) of UFH If quantity is unknown: give according to (aPTT) or give empiric dose of 25-50mg	**B**	Slowly IV over at least 1-3 min., not to exceed 50 mg in a 10 min. period.	**P**
Prussian Blue/ Radiogardase	Dirty bomb agents: radioactive cesium and thallium and non-radioactive thallium	150–250 mg/kg/d orally or via a nasogastric tube in 2–4 divided doses.	**C**	Prussian blue is dissolved in 50 mL of 15% Mannitol to treat constipation	**N P**

*** (AR) Availability requirements - ** Purchasable By MOH (P by MOH) Or Not Purchasable By MOH (Not NP by MOH)**

Antidote	Toxin	Dose	AR*	NOTES	P or Not P**
Pyridoxine (Vitamin B6)	- Isoniazid (INH) poisoning - hydrazine, and derivatives, and ethylene glycol overdoses	1 g of pyridoxine for each gram of INH ingested, to a maximum of 5 g or 70 mg/kg Unknown amount ingested: 4-5 g For Ethylene glycol poisoning: 100mg/day IV	B	A benzodiazepine should be used with pyridoxine in an attempt to achieve synergistic control of seizures	P
Sodium Bicarbonate	- Cardiotoxicity of xenobiotics that block Na channels (TCA) - Elimination Enhance of weak acids (salicylate, Phenobarbiturate, Methotrexate) - Correct life-threatening acidosis generated from toxic alcohols - Rhabdomyolysis	In TCA and salicylate: 1-2 mEq of NaHCO3 / kg IV can be repeated as needed to achieve a blood pH of 7.50–7.55.	A	It is a nonspecific antidote effective in the treatment of a variety of poisonings by means of a number of distinct mechanisms.	P
Starch	Iodine	15g starch in 500mls water orally.	A		P

Thiamine Hydrochloride	- Every potential alcoholic - prevent and treat Wernicke encephalopathy	Initial therapy: 100 mg daily. Up to 1000 mg of thiamine can be used in the first 12 hrs. if a patient demonstrates persistent neurologic abnormalities.	**A**	Given IM or IV	**P**
Vitamin K1 (phytonadione, phylloquinone)	Warfarin, and super-warfarin rodenticide	- **Oral Vitamin K1:** Marked prolongation of PT or INR without bleeding. - Adult: 50 to 100 mg/day orally initially in single or divided doses. - Pediatric: 0.6 mg/kg/day initially in single or divided doses. - INR or PT should be repeated measurement daily, and dose increased as needed to normalize INR or PT. **- Parental Vitamin K1:** Severe prolongation of PT or INR and frank bleeding. (*The patient should first receive fresh frozen plasma*) - Adult: 25-50 mg vitamin K1 iv infusion (diluted with D5W or 0.9% saline and infused slowly at a rate not to exceed 1 mg/min). - Pediatric: initial dose 0.6 mg/kg, titrated to response. Then, the dose should be repeated 2-4 times daily.	**B**	- IV Vit K has been associated with fatal anaphylaxis - If active bleeding use 4-factor prothrombin co-mplex concentrate), if available, afresh fro-zen plasma and Factor VIIa. - Complete reversal may not be desired in cases with medical indication for therapeutic antico-agulation.	**P**

*** (AR) Availability requirements - ** Purchasable By MOH (P by MOH) Or Not Purchasable By MOH (Not NP by MOH)**

Antidote	Toxin	Dose	AR*	NOTES	P or Not P**
PNI-ÈÀÕÅÿŘ ĬŘI-NdzÕÅÎdzYI-Õ	**Dabigatran** etexilate overdose Idarucizumab is licensed for use in adults when rapid reversal of anticoagulant effect of dabigatran etexilate is required as in emergency surgery or urgent proced - ures or life threatening or uncontrolled bleeding	5 g idarucizumab iv as 2 consecutive infusions of 2.5 g/50 ml over 5 to 10 minutes each or as 2 consecutive 2.5 g bolus injections. Administer a second 5 g dose may be considered in the following situations: •Recurrence of clinically relevant bleeding together with prolonged clotting times or •If potential re bleeding would be life threatening and prolonged clotting times are observed or •Patients require a second emergency surgery or urgent procedure and have prolonged clotting times. The safety and efficacy of Praxbind in children below the age of 18 years have not yet been established	B	-it binds specifically to dabigatran and not to any other anticoagulant -it can be used in conjunction with standard supportive measures -Hypersensitivity reaction may occur -Each 5g Praxbind contains 4 g sorbitol excipient, which could cause hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, acute liver failure in patients with hereditary fructose intolerance	NP
Polyethylene glycol (Macrogol '3350') Klean-Prep	Whole bowel irrigation for agents not bound by activated charcoal e.g. iron, lithium, also for body packers and for slow release preparations.	The solution is administered as 0.5L/hr in children < 5 years & 1-2 L/hr for adults. - It is administered by nasogastric tube or orally. - The end-point is recovery, and return of the drug to therapeutic levels	B	Contraindications: Extensive hematemesis, pa -ralytic ileus, bowel obst - ruction and, perforation or peritonitis.	P

Glucagon	- Beta blocker over dose - CCB overdose - Hypoglycemic agents overdose	β blocker toxicity: adult, Load: 3–5 mg. Higher doses may use if the initial bolus is ineffective (up to 10 mg)Maintenance: 2–5 mg/hr. (up to 10 mg/hr)Child: 0.15 mg/kg IV then, 0.05-0.1 mg/kg/h until improvement-In hypoglycemic toxicity: Adults: 1-2mg i.m. Child: 1mg in child >25kg,0.5mg if <25kg	**A**	Anticipate nausea and vomiting.	**P**
High dose insulin euglycemic therapy	-Severe calcium channel blocker poisoning ,severe beta blocker poisoning	Bolus of Regular Insulin 1U/kg then infusion at 0.5–1.0 U/kg/h. Give 25 gm (50 cc of D50W) initially then dextrose 0.5 grams/kg per h ; Titrate to euglycemia	**B**	-Monitor glucose frequently to prevent hypoglycemia. -Monitor serum potassium and replace as needed.	**P**
Penicillamine	Heavy metal poisoning (Lead, copper and arsenic)	Adult: 20-30 mg/kg/d, Initiating by 25% of this dose and gradually increase to the full dose over 2 -3 weeks. Maximum adult daily dose is 2 g. Child with mild to moderate lead poisoning, dose is 20 mg/kg/d	**C**	Penicillamine should be taken on an empty stomach	**P**

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LIST OF ANTIDOTES

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Notes

Notes

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